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CONTENTS

THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

announces

A Third Graduate Review Course

in

"Diseases of the Kidney and Genito-Urinary Tract"

on

MONDAY, TUESDAY, and WEDNESDAY
OCTOBER 26, 27, and 28, 1936

* * * *

A description of the course and an outline of the subjects to be covered will be found on page 245.

EXOPHTHALMOS*

A. D. Ruedemann, M.D.

Exophthalmos or proptosis is a common condition of the eye which is present in numerous general as well as in many local conditions, and its presence constitutes a valuable diagnostic sign. It requires careful study and serious consideration because it produces disturbing functional and organic changes and also a distressing cosmetic effect. Although much has been written on various special divisions of this subject, little attempt has been made to correlate the various types and to enumerate their essential differences.

The study of exophthalmos in a large number of patients with thyroid disease has given me a keen interest in the problems presented by this condition, and, in order to evaluate the findings, the entire subject has been reviewed. The following notes are the result of a study of the patients we have seen, plus a review of the literature.

The total volume of the orbit is approximately 30 cc. and the eyeball occupies one-fifth of the orbital space. The eye does not lie in the center of the orbit, but a little to the side of the midline and is near the base of the bony cone anteriorly-posteriorly. It does lie in the center of the vertical plane.

The eyeball moves in all directions and can be moved anteriorly, posteriorly, and, to a slight degree, vertically. Several instances of persons who have well established voluntary propulsion have been reported. The eye is raised, with the help of the superior rectus muscle, approximately 1 mm. on extreme elevation of the lid. It can be pushed forward in the socket by leaning forward, holding the breath, or by compression of the carotid artery. The apex of the cornea does not protrude beyond the superior rim of the orbit in normal persons. The cornea and the anterior orbital fascia form the base of the outer or bony cone; the eye forms the base for the inner or muscle cone. The orbital contents, with the eye, fill the entire space in the socket, and any change in cubical contents is bound to alter the position of the globe. A diminution in space by compression from without or an increase in contents by an increase in the orbital tissue results in protrusion, whereas a loss of tissue due to atrophy or an increase in space by removal of a wall results in the exophthalmos which is so commonly associated with trauma.

The orbit contains muscles, vessels, glands, and nerves, and also a considerable quantity of fat. These elements remain fairly constant in

*This is the first of a series of four papers on exophthalmos and protrusion of the eyeball. The remaining papers will be published in subsequent issues of the Quarterly.

any one person, except in advanced age when a loss of fat allows a definite sinking of the globe.

The lack of valves in the outflowing veins allows venous congestion to take place easily and rapidly in case of any increase in intra-orbital pressure. The lack of space for expansion, by virtue of the bony lateral walls, the association of the surrounding sinuses with thin walls, the brain cavity above and posteriorly, and the numerous other structural relationships make malposition of the eyeball a fairly common and important sign of disease in adjacent areas.

Methods of Measurement of Exophthalmos

The position of the eye should be estimated instrumentally and should be recorded for each individual case. Much effort and thought has been expended in trying to develop a universal exophthalmometer, but the variable factors exceed the constant factors so that relative rather than absolute values must be recorded and hence no definitely arbitrary limits of normal can be established.

Numerous instruments have been devised for the measurement of exophthalmos. A rough estimate of the degree of exophthalmos can be obtained by placing a ruler vertically from the brow to the cheek. This will not touch the cornea of an eye in the normal position, except in cases of myopia, and fairly accurate estimates are secured by this method. A testing frame with a flat lens can also be used, as can the ophthalmometer, by fixing the position of the head in the rest and measuring the necessary anterior-posterior movement of the mire case for each eye.

Instruments have been devised by Herring-Sattler which have been modified by Birch-Hirschfeld, and a more recent one by Kryosawa is patterned after a pelvimeter. The measurement is taken from the occipital protuberance and the tip of the other arm of the instrument is placed at the corneal apex. The objections to this method are the same as those to other instruments; namely, the individual variation in the structure of skulls, anteriorly-posteriorly, is too great to make possible an exact definition of the normal measurements.

In my studies, Hertel's exophthalmometer was used because it is simple to operate, relatively inexpensive, requires little time, is as accurate as any other instrument, and can be used repeatedly without replacement of parts.

It is my contention that each ophthalmologist should establish relatively normal values for the patients he examines, because the predominant race in any territory will aid in establishing the upper and lower limits of normal. After these have been established, he should then record the findings in each case. To measure the patient's eyes, the

vision should be fixed on the forehead of the examiner. Then, using equal pressure on both sides, one can accurately record the readings for any individual patient. The measurements thus obtained are of diagnostic significance. (In my own series of cases, I have measured each patient's eyes myself, so that the variable factor of individual interpretation has been eliminated.)

I have used ten groups of 100 patients each of so-called normals, consisting of cases for refraction, etc., and have established the following normal values for my own series: average values, O.D. 18.9 mm., and O.S. 18.7 mm., with a high normal of 20 mm. and a low of 14 mm. In some instances, the measurements have fallen below the scale of the instrument, and in some cases of exophthalmos, they have been beyond the upper limit of the scale, which is 33 mm.

Measurement of the width of the palpebral fissures is also useful. Here the variables are not so numerous or so great as in the anterior-posterior position. In the same series of normals, a ruler held across the middle of the cornea, with the patient's vision fixed on a distant object, yielded a measurement of 9 mm. O.U. Any exposure of the sclera above and below the cornea usually arouses suspicion that there is some protrusion of the eye or widening of the fissures. This measurement is important because many cases of so-called exophthalmos, especially "photographic" exophthalmos, are found to be merely a widening of the palpebral fissure. Hence a photograph without specific measurements is valueless in the diagnosis of exophthalmos. Relative ptosis, such as is seen in some instances of thyroid disease and in some patients with exophthalmos, makes it advisable to record the fissure measurement.

A measurement of the size of the pupil should be included in the study of each patient, as this aids in the diagnosis of certain other conditions and can be made easily when the other measurements are being recorded.

Visual estimation of the amount of proptosis is more inaccurate than is the finger tension in cases of glaucoma. The mere statement that the patient has exophthalmos without any record of the measurements is likely to be misleading and has caused, and is still causing, confusion, especially in the selection of cases for thyroid operations.

Diagnosis of Exophthalmos

A patient presenting signs of exophthalmos requires a thorough examination. I have established the following routine procedure in making the diagnosis in these cases.

1. Careful history, especially as to familial characteristics of eye position (particularly in patients with hyperthyroidism), and information concerning onset and duration of symptoms.

2. Vision—external examination.

3. Measurements—exophthalmometer, fissures, pupils.

4. Mobility of globe—diplopia, muscle measurements.

5. Refraction—ophthalmoscopic examination.

6. Intra-ocular tension.

7. Examination of fields (if indicated).

8. Location of pain and tenderness.

9. Temperature, blood counts including differential counts, urinalysis, Wassermann reaction.

10. Roentgenograms of orbit, sinuses, optic canal, and skull.

11. Physical examination in all cases of bilateral exophthalmos and in all but exceptional cases of unilateral exophthalmos including examination of nose and throat and determination of basal metabolic rate, etc.

12. Photographs of eyes, with measurements.

Classification of Exophthalmos

The cases are divided into two main groups, (1) bilateral and (2) unilateral exophthalmos. After a careful study of my series of cases, and fairly diligent search of the literature, I have been able to list the following diseases of which exophthalmos is a sign.

Bilateral Exophthalmos

A. In children

I. Hemorrhage
- a. Newborn, trauma
- b. Spontaneous, as in hemophilia and blood dyscrasias
- c. Scurvy

II. Increase in orbital content
- a. Hemangioma, tumor, etc., (rarely bilateral)
- b. Leukemia, chloroma, lymphatic edema, etc.
- c. Xanthomatosis (Schüller-Christian disease and diabetes insipidus)
- d. Tenonitis
  1. Serous
  2. Purulent
- e. Endocrine disorders
  1. Hyperthyroidism
  2. Hypothyroidism

III. Decrease in size of orbit
- a. Tower skull
- b. Hydrocephalus

B. In adults
  I. Hemorrhages
    a. Spontaneous leukemic, arteriosclerotic
    b. Traumatic
    c. Asphyxia
    d. Scurvy
  II. Increase in orbital content
    1. New tissue
      a. Leukemia
        1. Mikulicz's disease
        2. Chronic lymphoma
        3. Lymphoblastoma
      b. Bilateral tumor masses
    2. Edema, venous stasis, etc.
      a. Trichinosis
      b. Tenonitis
        1. Serous
        2. Purulent
      c. Cavernous sinus thrombosis and stasis
      d. Hyperthyroidism
      e. Malignant exophthalmos
      f. Hypothyroidism
      g. Hypertension
      h. Allergic conditions
      i. Arteriovenous aneurysm (orbital and cerebral)
  III. Decrease in size of bony vault of the orbit
    a. Paget's disease
    b. Leontiasis ossea
    c. Acromegaly
  IV. Relaxation of orbital fascia and muscle paralysis
    a. External ophthalmoplegia

Unilateral Exophthalmos

A. In children
  I. Hemorrhage
    a. Newborn, trauma
    b. Spontaneous
    c. Scurvy
  II. Increase in orbital contents
    1. Inflammatory
      a. Panophthalmitis
      b. Orbital cellulitis (sinus disease)
      c. Pyocele, pyemic abscess

d. Cavernous sinus thrombosis; lateral sinus thrombosis
e. Periostosis, osteitis
f. Tenonitis
    1. Traumatic—surgical, foreign bodies
    2. Infectious
g. Foreign bodies

2. Non-inflammatory
a. Intermittent (vascular)
b. Encephalocele
c. Meningocele
d. Dermoid cyst—teratoma
e. New growths
    1. Sarcoma
    2. Hemangioma
    3. Mucocele
f. Brain tumor

B. In adults

I. Hemorrhage
a. Spontaneous—leukemic, arteriosclerotic
b. Asphyxia
c. Scurvy

II. Increase in orbital content

1. Inflammatory
a. Cavernous sinus thrombosis; lateral sinus thrombosis
b. Orbital cellulitis
c. Pyocele
d. Periostitis
e. Tenonitis
    1. Serous
    2. Purulent
f. Panophthalmitis
g. Foreign bodies
h. Granuloma—actinomycosis, mycelium, blastomycosis
i. Hydatid or echinococcus cyst
j. Pseudotumors
k. Tumors
    1. Gumma
    2. Tuberculoma
    3. Carcinoma

2. Non-inflammatory
a. Air
b. Allergic conditions
c. Osteoma

d. Pulsating exophthalmos (may also be inflammatory)
   1. Trauma (77 per cent)
   2. Spontaneous (23 per cent)
e. Intracranial aneurysm

III. Decrease in size of orbit
a. Trauma
b. Hyperostosis, exostosis
c. Paget's disease

Bilateral Exophthalmos in Children

In the study of bilateral exophthalmos in children, several interesting facts present themselves. The first three diseases outlined—the hemorrhagic blood dyscrasias and scurvy—produce intra-orbital hemorrhages. The next four—hemangioma, leukemia, xanthomatosis and tenonitis—produce new tissue. In three of these—chloroma, xanthomatosis and lymphatic edema—the new tissue is formed directly from the blood elements. The tumors which cause exophthalmos are often hemangiomas, but any type, such as sarcoma, fibroma, and those of neurogenous origin may be found. When exophthalmos in children is due to an endocrine disturbance, the onset usually is later than in the other diseases listed, although the age of onset for various conditions cannot be set definitely. In either hyperthyroidism or hypothyroidism, the major problem is in the thyroid gland, but the general glandular system is severely involved; also the last two groups, tower skull and hydrocephalus, are definitely associated with physical changes in the skull which produce exophthalmos by making the orbit saucer-shaped, and by decreasing its volume content.

Hemorrhage

Trauma in the newborn: Bilateral exophthalmos in the newborn, due to hemorrhage, is rare, but several cases have been reported. Most instances of proptosis caused by hemorrhage are unilateral, but the possibility of this condition must be kept in mind also when both eyes are affected. Instrumentation, the use of forceps, or a prolonged delivery, especially in a primipara, may produce sufficient orbital hemorrhages in the infant to push the eye forward. These hemorrhages tend to clear rather rapidly, although the frequently associated cerebral disturbances which are evidenced by convulsions, etc., may possibly produce blindness, weakness, or paralysis. The ocular signs are transitory, the history usually is definite, and the diagnosis is not difficult.

Hemophilia and other blood dyscrasias: I have never observed a case of bilateral exophthalmos in a patient with hemophilia, but several such instances have been reported in the literature, and hence attention must

be called to this possibility in differential diagnosis. This blood dyscrasia, which is transmitted by the mother, is confined to male children only, and they may suffer severe hemorrhage from any trauma, however slight. The oozing usually is prolonged and of capillary origin. Cuts and lacerations generally are the precipitating cause of hemorrhage in these patients, contusions are next in importance, and spontaneous hemorrhages are rare. The history usually suffices to establish the diagnosis. Either eye may be affected by exophthalmos due to hemorrhage, but it is rare that both are involved at the same time.

Hemorrhages due to leukemia rarely produce bilateral exophthalmos, although the possibility must be taken into consideration. The diagnosis can be made from the blood picture. Examination of the fundus reveals engorgement of the veins and, at times, hemorrhages.

Scurvy: One of the causes of exophthalmos early in life is scurvy which is due to lack of vitamin C. This deficiency disease appears when there is a lack of breast milk, usually as the baby is being weaned, and before the proper formula for feeding has been determined. Naturally it is most prevalent in families afflicted with poverty or ignorance. Children less than one year old are most frequently affected, although instances in older children have been reported, especially in times of depression and among the poorer classes.

Associated with the proptosis and of even more frequent occurrence in scurvy are disturbances in the epiphyseal junctions of the bones of the legs. Early flexion of the legs is followed by eversion and immobility, and finally, by a state of pseudoparalysis. Diarrhea is also an accompanying symptom.

The pathologic basis for the hemorrhage in these patients presumedly is a lack of cement substance in the endothelial cells of the blood vessels, which makes them extremely permeable. The seat of the hemorrhage producing the exophthalmos usually is between the orbital plate and the periosteum. The hemorrhage invades the upper lid, and comes on suddenly following a trifling injury or a fit of coughing or crying. There is a statement in the American Encyclopedia of Ophthalmology that a black or protruding eye which occurs during the first dentition and is not due to injury is more likely to be due to scurvy than anything else.

The eyeball, usually on the left side, is pushed downward, forward, and laterally. The amount of proptosis is slight, whereas the lid eccymosis may be great. The other eye may not be involved for several days or until after the condition of the first eye has begun to improve. No local orbital treatment is advisable because pressure and manipulation produce additional hemorrhage. Rest and the proper diet are the essential factors in treatment. The antiscorbutic diet, which includes

large quantities of lemon juice or orange juice, begins to effect recovery within four to five days. However, the treatment must be prolonged, or additional hemorrhages may occur.

Increase in Orbital Content

Tumors, hemangiomas, etc.: The tumorous conditions which produce bilateral increase in the orbital content are not numerous, and new growths are rarely found simultaneously on both sides. However, a few such instances have been reported, the diagnosis usually being made at the time of operation. Multiple dermoid cysts or hemangiomas might be suspected in cases of bizarre bilateral exophthalmos. In such conditions, the proptosis would not be typical of the bilateral exophthalmos seen in other diseases.

Leukemia, chloroma, lymphatic edema, etc.: Invasion of the orbit by overproduction of the blood elements fortunately is rare. The cases reported and the three or four that I have seen all have terminated fatally. Probably the most common and also the most spectacular growth of this type is the chloroma which is seen in myelogenous leukemia. It derives its name from the greenish coloration of the skin and tumor mass. Much conjecture regarding the etiology of these growths and their true classification is found in the literature. They probably have their origin in an acute leukemia with a predilection for the periosteum, especially in the cranium. The leukemia is of malignant type and the cells apparently have the power to multiply in the blood stream and tissue spaces. Various forms of cells are described. These range from the large lymphocytic and atypical forms to the aleukemic forms, which are the more malignant. The anemia is due to the crowding out and replacement of the erythrocytic blood elements and lessening of red cell formation. The malignancy of the tumor depends on this replacement factor.

The points of interest to the ophthalmologist are that the exophthalmos usually commences in one eye, with rapid subsequent involvement of the other orbit. The invasion by the tumor may be posteriorly or from above. The mass is made up of a greenish tissue substance, which fades rapidly on exposure to air, supposedly as the result of the oxidation of the bilirubin it contains. Accompanying signs and symptoms are weakness, anemia, headaches, tinnitus, deafness, and changes in the blood indicating leukemia.

The blood picture shows a red count in the neighborhood of 3,000,000 and hemoglobin from 70 to 80 per cent. The differential count shows an increase in the mononuclear leukocytes and in the large and small lymphocytes.

Removal of the tumor masses and treatment by radium and roentgen radiation are merely palliative. No cures have been reported in this type of case.

Other forms of leukemic tumors have been described as causing exophthalmos. Major Wright reported a case of lymphoblastoma in which there was an increase in the mononuclear cells (monocytes and transitional cells). The patient, a child twelve years of age, had bilateral orbital growths, although only the left eye was proptosed. The boy died within a short period after he was observed.

The so-called lymphomas may produce bilateral protrusion of the eyeball, and diagnosis is difficult because of lack of signs and symptoms of systemic disease. The blood picture may not be strikingly abnormal, and, unless the tumor is sectioned, evidence of the true diagnosis will be entirely lacking. In this type of case, it often is necessary to have blood counts made repeatedly, for the cells may vary from time to time and several examinations may be required to reveal an increase in white cells.

Xanthomatosis (*Schüller-Christian disease*), *Lipogranuloma:* The rarity and uncertainty of knowledge concerning a disease may sometimes be estimated by the number of titles attached to it. This disease, first designated as xanthoma by Rages in 1836, has been described repeatedly since then. Excellent discussions of the subject by Wheeler, Knapp, Heath, and Rogers are to be found in the literature on ophthalmology. Several subdivisions of this condition, such as Gaucher's disease and Niemann-Pick disease, are grouped under lipoid dystrophies but these are not accompanied by exophthalmos.

Exophthalmos due to xanthomatosis is becoming more familiar to oculists and is being diagnosed more frequently; hence it may be expected that more descriptions of cases of this type will be recorded in the literature. Personally, I have seen two cases, one in a young girl, and one in a young boy. The disease occurs most frequently in children; only six of the fifty-five patients reported in the literature were more than twenty years of age. Remissions and relapses characterize the condition and new points of invasion may be evident at any time.

The cases reported represent all types of this disease, according to the parts involved. The eyeballs usually are pushed straight out by a mass of fibrofatty tissue in the orbit. This tissue is lipogranuloma, made up of three major portions, foamy lipoid cells, inflammatory cellular exudate due to tissue reaction, and fibroblastic proliferative tissue.

There may be map-like changes in the skull, due to a pressure atrophy by the histiocytes. In some patients, the pituitary gland may be involved in the process with resultant diabetes insipidus. Extreme thirst and fre-

quent micturition, a sore mouth, loose teeth, dwarfism, amenorrhea, pathologic fracture, discharge from the ear, anemia, and shortness of breath constitute signs and symptoms of this condition. Many variations are noted in individual cases, and neither exophthalmos nor diabetes insipidus are essential to the diagnosis of xanthoma.

The disease is caused by faulty lipoid metabolism and little is known of its etiology. About 30 per cent of all cases terminate fatally. Roentgen irradiation associated with a diet low in fats and plenty of exercise to increase metabolism has offered the best therapeutic results. Defects in the bone may completely heal following this regimen.

Bilateral tenonitis: Bilateral serous tenonitis is a rare condition producing but slight degrees of exophthalmos, although the disturbances in the orbit are severe. The discomfort of the patient is out of all proportion to the extent of the edema in the anterior portion of the orbit. The process usually begins in one eye and may be present merely over one small area. The conjunctiva is edematous and pale yellow in color. Movement of the globe causes pain. As the disease progresses the patient may have a slight fever. A little later, the other eye may become involved and the entire course of the disease may last from several days to a week. The eyes are exquisitely sensitive and the patient refuses to move the eyeballs.

Treatment consists of the use of salicylates, heat, and general supportive measures. The prognosis is good.

I have seen one patient with bilateral tenonitis which was due to diabetes and the eye condition cleared promptly when the patient became sugar-free.

Purulent tenonitis usually is unilateral following injury, although I have seen one patient in whom the process was bilateral following tenotomy of one eye. Extreme exophthalmos developed which resulted in some loss of sight in both eyes.

Endocrine disorders (Hyperthyroidism, hypothyroidism): Bilateral exophthalmos in children does not occur frequently, and, in my own experience, endocrine disturbances have accounted for most of the cases. These conditions are described fully under the classification of exophthalmos in endocrine diseases in adults, and hence no detailed discussion will be presented here. I shall merely mention that in nervous, irritable children who are not gaining weight, and who show signs of widening of the fissures with slight protrusion of the eye, hyperthyroidism must be considered. On the other hand, those who gain weight easily, are slow in motion and thought, and have heavy eyelids, may well belong in the group with hypothyroidism.

Both these groups of patients present interesting problems to the ophthalmologist. For the treatment of instability of the ocular muscles, exercises frequently are ordered which prove of no value. This muscle instability varies from day to day and must be central nuclear in origin rather than peripheral. Some of these children are referred by school authorities for eye examination, especially for the fitting of glasses. The frequency with which glasses are obtained is a good indication of the general lack of knowledge in regard to diseases of this type in children. In our series of cases of exophthalmos due to thyroid disease in both adults and children, 75 per cent were wearing glasses at the time of examination. These had been prescribed during the course of the disease, and some patients had even received several pairs, while the exophthalmos continued to progress.

Protrusion of the eyes may be just as marked and just as serious in children as in adults, and it is important to realize that although some of these children require operations on the thyroid gland, others may be benefited by rest in bed and general measures, including glandular therapy. Great care and judgment must be exercised in the treatment of these conditions, for many of the general symptoms may be transitory. The unwise use of glandular extracts and other therapeutic measures may precipitate more serious difficulties in these patients. Thyroid extract and the new pituitary products should be prescribed only by those with considerable experience in clinical endocrinology.

Decrease in the Size of the Orbit

Tower skull: A variety of congenital malformations of the skull may involve the orbit. In some instances, the deformity is slight and in others extreme, with the head pointed and the eyes almost luxated. This is accompanied by loss of vision, cerebral deficiency, and other associated signs and symptoms which include optic atrophy, nystagmus, headaches, convulsions, and hyperopia.

The disease is not commonly reported to cause exophthalmos but this is because of lack of recognition rather than lack of frequency. Since the excellent report by Davis in 1925, eight patients have presented themselves at the Cleveland Clinic with exophthalmos which might be classified as resulting from this malformation.

The two forms most often described are the dome-shaped, tall head, and the extremely high, pointed type. Schüller mentions three forms, the tower skull, the short, broad head, and the abnormally high, pointed type. Exophthalmos, although rather rare, has been reported to accompany all three types; frequently in the first, and less often in the second and third groups. One reason for this is that most authorities classify

all these deformities under the first group, tower skull, and do not refine their definitions.

The etiology of these malformations is unknown. Syphilis was not the cause in any of our eight cases nor in the six that Davis described. Some fault in development produces the deformities these patients display, as other congenital anomalies, such as webbed fingers and toes, cleft palate, medullated nerve fibers, etc., often are present. Males are more frequently affected than females. The mental disturbances are probably not due to stenosis of the brain, but rather to a combination of malformation of the brain and lack of development of the skull. Wiggers maintains that the bone grows around the tissue and fits it, and that the tissue does not expand to fit the bone.

A patient with hyperopia, secondary optic atrophy, and nystagmus may have a mild form of this disease, and the exophthalmos may vary from that of slight degree to actual luxation. This suggests the vast number of types and combinations of eye symptoms and signs which may be present in these patients.

The orbit becomes saucer-shaped, the roof is almost vertical and the lesser wing of the sphenoid is vertical rather than horizontal. The orbit may be further shortened by pushing forward of the greater wing of the sphenoid. The entire picture is one of a short orbit with insufficient room for its contents. Nystagmus is of the visual type and may have its origin in congenital amblyopia or may be due to visual deficiency of postneuritic or hyperopic origin.

Cranial deformities revealed by roentgenographic examination are numerous and include (1) the high-domed, pointed skull, (2) the severe form with a short anterior-posterior diameter, (3) wide, bulging, temporal fossae, (4) shallow orbits, (5) high, narrow palate, (6) deviation of the nasal septum, (7) facial asymmetry, and (8) honeycombed skull due to convolutional markings and cerebral pressure.

The malformation may cause headaches due to the cerebral stenosis or to the visual defect. These patients also have muscle and refractive errors. Convulsions were not seen in any of our patients, and are rare.

Treatment should be directed toward the cerebral cavity. Decompression, if performed early, may benefit the patient, although death following operations is not unusual in these cases. Fenton has made a plea that these patients be treated early and he believes that radical measures are justified, because of the patient's extreme hideousness and the progressive cerebral decline and continued visual loss.

Hydrocephalus: Hydrocephalus is encountered quite frequently in a diagnostic clinic where there is a neurologic surgeon, and I have seen numerous cases of both internal and external hydrocephalus. Exoph-

thalmos is not a major sign in this condition, and is seen but rarely. When present, it usually is bilateral and is produced by a pushing forward of the floor of the orbit. In contrast to tower skull, the sutures in hydrocephalus may be open, and this, although allowing tremendous enlargement of the skull, protects the orbit.

Associated with the enlargement of the head may be edema of the discs with either primary or secondary atrophy of the optic nerve.

Roentgenograms reveal the relative increase in size of the various parts of the cranium and ventriculography reveals the extent of the fluid increase. Various treatments have been devised for this condition, and at present it appears that several of these methods offer considerable promise.

Summary: In considering the entire group of children with bilateral exophthalmos, roentgen examination is of value in four, namely scurvy, xanthomatosis, tower skull, and hydrocephalus. Blood studies yield important information in scurvy, the leukemias (chloromata) and possibly in xanthoma, if the cholesterol is increased. The basal metabolic rate is of importance in the diagnosis of exophthalmos due to increased or decreased activity of the thyroid gland.

Almost all cases of bilateral exophthalmos are systemic in origin and hence a careful physical examination may reveal the diagnostic clue.

PULMONARY TUBERCULOSIS

BERNARD H. NICHOLS, M. D.

The origin of tuberculosis probably dates back to the days when men first began to live in compact social groups. Through studies of Egyptian mummies, Derry, Wood, Jones, Armand Ruffer, and Elliott Smith have shown how this scourge wrought havoc among the people even in the time of the Pharaohs. The Veda of India, the Zend-Avesta, sacred book of the Parsees, the works of Hippocrates, of Celsus, of Aretaeus of Cappidocea in 70 B.C., and the writings of Avicenna all abound in discussions of phthisis. The American Indians of pre-Columbian times apparently were free from tuberculosis, for no indication of its existence is to be found in any of the thousands of well-preserved skeletons of the various tribes. This is conclusive evidence that the continental peoples were later responsible for the development of the disease in North America.

It was not until the eighteenth century that the disease received the name by which it is now known—tuberculosis. Reid, the English physician, in 1782, and Baille in 1793, called attention for the first time to granulation and tubercles which increase in size, coalesce, and develop perfect cavities. However, Laennec, who at the age of 35 was himself a victim of the malady, laid the real foundation for our understanding of the pathological anatomy of tuberculosis. He said: "Tuberculous matter can develop in the lungs and other organs in two principal forms: as isolated bodies (granulation, miliary tubercle, non-caseous tubercle, caseous tubercle, ulceration or cavity), and an infiltration." Laennec was the originator of the method of mediate auscultation by which he learned to detect the development of tubercles in the living subject, and humanity will always be grateful to him for having created the first means of diagnosing the disease. The infectious nature of tuberculosis was obvious to him, for he wrote, "There is perhaps no organ which is immune against the development of tubercles," and "Pulmonary tuberculosis is the result of secondary extension, glands being a primary foci."

In 1865, Villemin furnished positive proof of the inoculability of the tubercle and of caseous material. In his address before the Academy of Medicine in Paris, December 5, 1865, he drew the following conclusions:

"Tuberculosis is a specific affection.

"Its cause lies in an inoculable virus, and it should be classed with syphilis or near glanders."

It then remained to demonstrate the virulent agent by the methods originated by Pasteur. This was done by Robert Koch (1843-1910), a German district physician in Wallstein, Germany, whose name remains gloriously associated in the literature with the study of tuber-

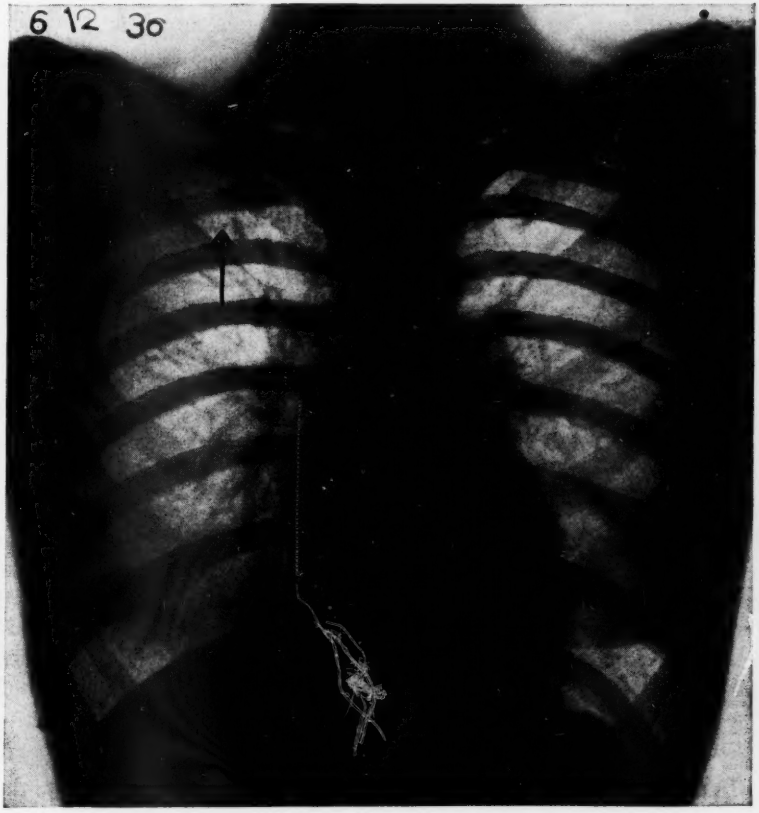

FIGURE 1.—Incipient pulmonary tuberculosis.

culosis. He published a paper on the "Etiology of Anthrax," which is memorable as the starting point of a new method of research into the causation of infectious diseases. He demonstrated the constant presence of germs in cattle dying from this disease, but the epoch-making advance of Koch was to grow those organisms in a pure culture outside the body, and to produce the disease artificially by inoculat-

ing animals with the cultures. Koch is really our medical Galileo, who, by means of a new technique—pure cultures and isolated staining —introduced us to a new world. Upon these two memorable researches made by a country doctor rests the modern science of bacteriology. Before Koch's discovery of the tubercle bacillus, we were helpless and hopeless; in an Oriental fatalism we accepted with folded hands a state of affairs which use and wont had made bearable. Today, look at the contrast! We are both helpful and hopeful.

The tubercle bacillus is a slender, non-motile, rod-shaped organism having an average diameter of one-half to one-quarter of the diameter of a human red blood cell. It is reproduced by elongation and transverse division of the rods, and not by sporation. The organism is particularly resistant to cold and may retain its vitality at the temperature of liquid air. Moist heat at 95° C. for a period of at least one minute is necessary for its destruction. Dried sputum on slides or gauze, when left in dark places at a low temperature, has been virulent after from two to four months. Gaertner found the organism alive and active in the cadaver 167 days after burial. The chemical resistance also of the organism is interesting, a 1:100 solution of potassium iodide, a 1:900 solution of boracic acid or a 5 per cent solution of carbolic acid for a period of five minutes being necessary for its destruction. A 1:1000 solution of bichloride of mercury for one hour or a 1:10,000 solution for twenty-four hours will kill the organism.

The reaction of the human body to the invasion of the tubercle bacilli is usually evidenced by the presence of a tubercle. It is evident that the tubercle is not formed by proliferation of fixed tissue elements in response to irritation, but its formation is a uniform attack upon an invading enemy carried out in a uniform manner no matter what organ or tissue is invaded. The tubercle always attacks a lympathic cell. First, the bacillus is taken up by the polynuclear leukocytes which soon undergo degeneration and death, and these form groups which are surrounded by large mononuclear leukocytes and in turn fuse to form the typical giant cell.

In the lung there is an early exudation of lymphatic elements into the alveoli which are analogous to those found in the intralymphatic tubercles. Coalition of these tubercles produces an increase in size of these areas and results in tuberculous pneumonia which may be followed by resolution or caseation. This caseation of tubercules is believed to be due to the direct and localized toxic action of the bacilli and their diastatic or toxic secretions upon the giant cells which contain them. This action produces an isolated area of tuberculous pneumonia which is followed closely by caseous bronchopneumonia as the fixed

cells of the lung succumb, and cavitation may result. A tuberculous tubercle, therefore, is truly a lymphatic production, the fixed cells in the organ in which the tubercle develops playing no part in its histogenesis.

Pulmonary tuberculosis is the type which is of most frequent occurrence in man as well as in cattle. This does not imply that this type is

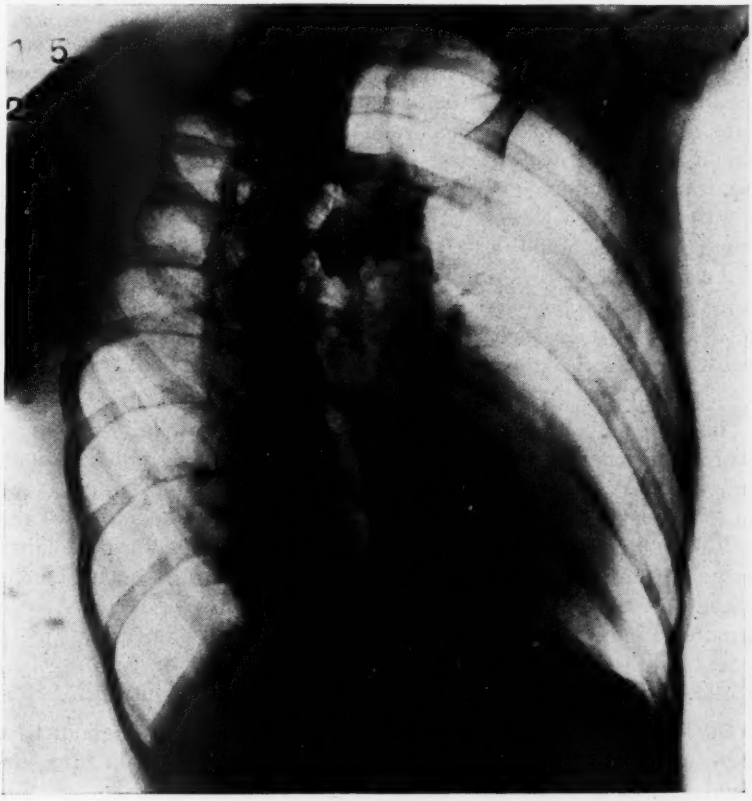

FIGURE 2.—Quiescent tuberculosis.

first from the standpoint of priority of infection, as it is in reality of a later date and is consequent to the formation of a gland in the cervical, tracheobronchial, or mediastinal group. Circulation is less rapid in the loose connective tissue which surrounds the alveoli and small bronchi, the lymph spaces, and the capillaries than is the case in any other organ. This is particularly true of the apices and the smaller vessels which have a lesser degree of elasticity, and adherence to the walls of

the lymph and blood capillaries occurs here with greater intensity than elsewhere. The presence of pleural effusion without a definite logical cause should be considered an evidence of tuberculosis. Frequent attacks of pleurisy in cases of pulmonary tuberculosis are undoubtedly due to the presence of a direct communicating pleural lymphatic system with the lungs.

Mechanism of the Infection

The skin may be a portal of entry for the organism. Holt collected forty-one cases of tuberculosis following circumcision. The mucous membrane is a very fertile field, especially the ocular mucous membrane. The nasal mucous membrane is not a common source of infection on account of its continuous, active phagocytosis. The respiratory tract is not of as much importance as a means of transmitting the disease as was formerly believed. The tonsils probably form an important source of infection and the gastro-intestinal tract may be considered to be the most common portal of entry. Infection by any of the above means results in a primary tubercle bacillus septicemia, except possibly the disease is contracted by direct air inhalation when the tubercle bacilli may also be transmitted subsequently by the lymphatics or the blood stream.

The extremely frequent occurrence of pulmonary manifestations in tuberculosis has led to the belief that this disease is transmitted through the respiratory passages. Primary pulmonary tuberculosis may occur either by way of the air passages, that is, by direct inhalation of the bacillus in the air, or by way of the blood stream. We believe the latter means of transmitting the infection is by far the more frequent. Some leukocyte containing its parasitic bacilli, which have recently been introduced into the body or derived from a focus of infection of more or less long standing, is arrested in the interalveolar or peribronchial capillaries and becomes the point of departure for a giant cell.

The lung is divided into lobules, each having a capacity of about 1 cc. These lobules are surrounded by connective tissue which in turn surrounds lymphatic spaces. Early involvement of these spaces was observed by Dunham and resulted in the "Dunham Fan," which may be demonstrated on the roentgenogram as a fan-shaped infiltration.

Albrecht and Anton Gohn concluded that an involvement of the bronchial lymph nodes is always accompanied by a corresponding lung lesion, the latter being the primary site of inoculation. Marfan, Weigert, Bollinger, Calmette, and others, however, have proved definitely by inoculation through the mucous membrane of the eye that the glands of the hila are involved first and that the lung lesion is a secondary manifestation. It is evident that a true Gohn primary infection must

be only air-borne. It is contrary to the present consensus of opinion that an air-borne infection is of as easy accomplishment as an infection by other routes.

If it happens, however, that the infecting bacilli are isolated, if they are few in number, or not very virulent, the leukocytes by which they

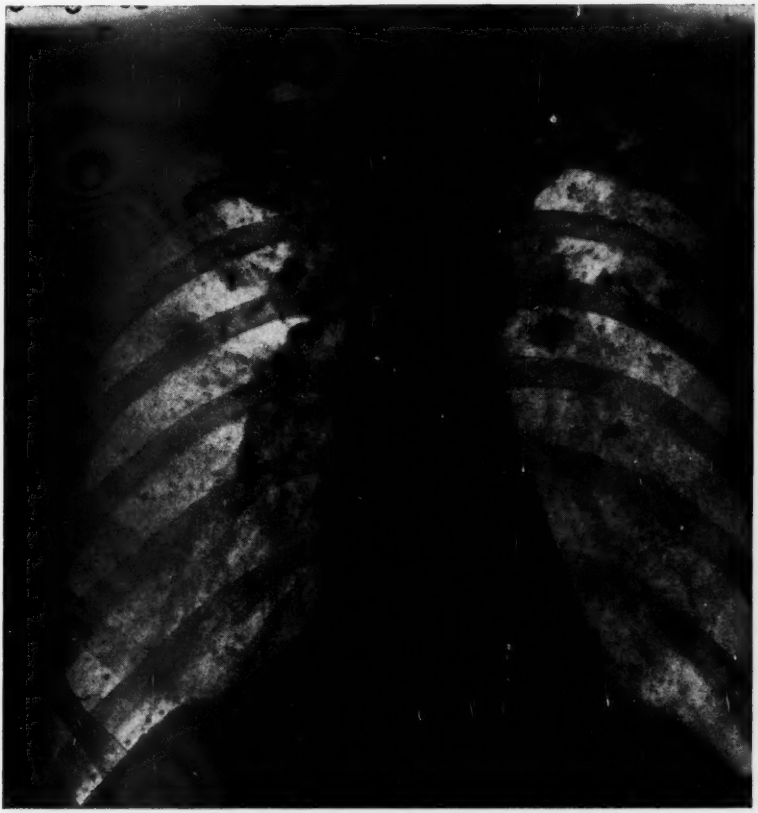

FIGURE 3.—Miliary type of tuberculosis, calcified.

are ingested remain unharmed for a long period despite the presence of these undigested parasites in the cell protoplasm; they preserve their motility and continue their migrations in the lymph or blood circulation throughout the various organs up to the time when, sooner or later, they die. Then at the point where the dead cells form a capillary embolus, perhaps far removed from an obscure portal of entry of the bacilli, a tuberculous lesion develops. Thus, following a nonmassive

infection, no matter of what origin—whether produced by an excoriation of the skin, occurring in a healthy mucous membrane, or transmitted by way of the respiratory passages or by the intestine—there appears occasionally an isolated localization of tubercle bacilli—in the lung, pleura, joint, kidney or other serous membrane, bone, testicle or ovary, or the larynx. The lung, however, is most likely to be the seat of this localization because of the immense surface which it presents for the development of a blood and lymph capillary system which, in the lungs, is more extensive and delicate than in any other organ.

The frequent occurrence of so-called primary tuberculosis of the lung is due, therefore, to the fact that primary tuberculosis represents the first manifestation of a bacillary infection which may have occurred by way of any lymphatic or blood route, often long before the appearance of other signs of the disease, and which may possibly have remained dormant for years.

Diagnosis

Time was, and this within memory of the living, when a diagnosis of consumption in an adolescent patient was rightly regarded as a sentence of death. The "churchyard cough" was the inevitable prelude to the grave. If we may judge this period by the novelist, consumption was the normal fate of a youth attended by beauty, but the lady of the Camellias might have looked forward to a disreputable old age had she lived today.

It was a pupil of Corvisart, Rene Theophile Laennec, who laid the foundation of modern clinical medicine. The story of his life is well known. A Breton by birth, he had a hard, uphill struggle as a young man—a struggle with tuberculosis of which we have only recently been made aware by the publication of a charming book by Professor Rouxeau of Nantes—"*Laennec avant 1806.*" Influenced by Corvisart, he began to combine the accurate study of cases in the wards with anatomical investigations in the deadhouse. Before Laennec, the examination of a patient had been largely by sense of sight, supplemented by that of touch, as in estimating the degree of fever, or the character of the pulse. Auenbrugger's "*Inventum Novum*" of percussion, recognized by Corvisart, extended the field, but the discovery of auscultation by Laennec, and the publication of his work—"*De l'Auscultation Mediate,*" in 1819, marked an era in the study of medicine. The clinical recognition of individual diseases had made really very little progress; with the advent of the stethoscope began the day of physical diagnosis. The clinical pathology of the heart, lungs, and abdomen was revolutionized. Laennec's book is in the category of the eight or ten greatest contributions to the science of medicine. His description

of tuberculosis is perhaps the most masterly chapter in clinical medicine. This revolution was effected by a simple extension of the Hippocratic method from the bed to the deadhouse and by correlation of the signs and symptoms of a disease with its anatomical appearances. The method of diagnosis of pulmonary tuberculosis by evaluation of the history and physical findings, namely auscultation and percussion,

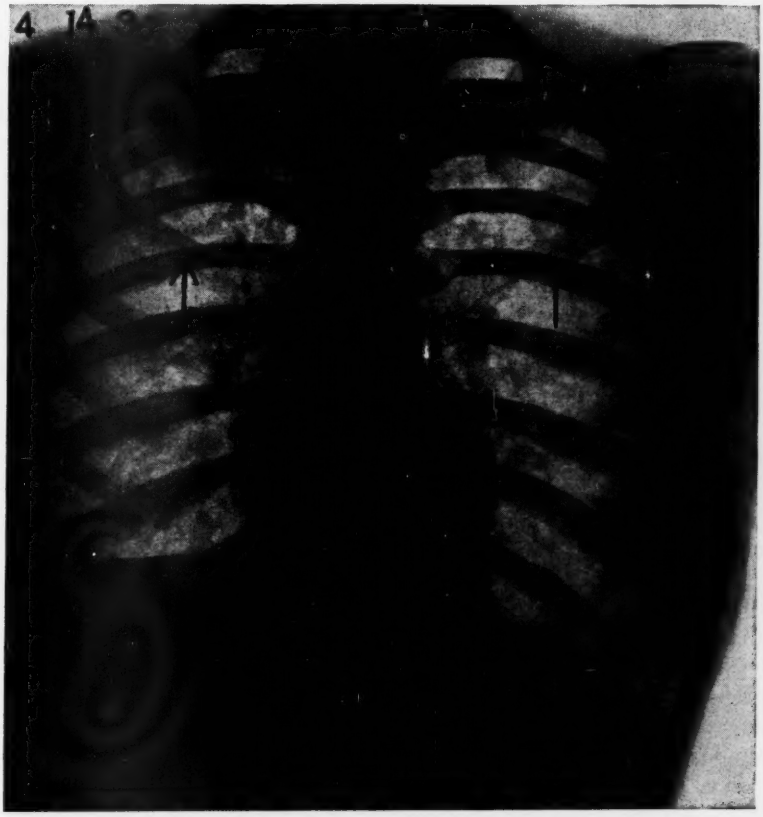

FIGURE 4.—Active pulmonary tuberculosis with cavitation.

was used for many years. Then came the discovery of the x-ray which resulted in earlier recognition of the disease and greater accuracy in diagnosis.

Roentgen examination: In 1896, Wilhelm Conrad Röntgen discovered the x-ray and it was learned soon after this that roentgenograms of the chest were of the greatest value in the diagnosis of pulmonary tuberculosis. Fortunately, not all infections of the chest terminate in

caseous bronchopneumonia and cavitation. The vast majority of the infections result in fibrosis, calcification, or both, and thereby the process is arrested. We feel this is the proper expression, as many calcified lesions contain live bacilli and may show exacerbation of the disease at any time. Fibrous and calcific deposits may be well demonstrated by roentgen examination.

Miliary tuberculosis is evidently a blood stream infection and the lesions are interstitial in character, and part of a general infection in which many other organs are involved. This type of tuberculosis usually produces little or no physical signs and the characteristic, small, soft, nodular infiltration observed on the roentgenogram is of the utmost importance in diagnosis. We might well quote here, "Tubercules must be seen and not heard." (Dr. James Alexander Miller.)

This method of chest examination is the most important single factor in the determination of the presence and extent of pulmonary tuberculosis. Since the chest is an air-containing cavity, it can readily be examined by use of the roentgen ray. However, the interpretation of roentgen films of the chest in many cases, particularly in children, is extremely difficult and no attempt at such a diagnosis should be made unless a physician has had proper training. The first and most important basis for such a training is an understanding of all the changes which may take place after a tuberculous infection has been established in the chest.

The first change with which the roentgenologist should be familiar is exudative infiltration. This is nature's first reaction to the infection and always means an active lesion. This may continue for a considerable time before any physical signs can be elicited. These exudative, infiltrated areas may be single tubercles or groups of tubercles; if such grouping or coalescing of tubercles takes place, the presence of a caseous bronchopneumonia will occur and this is often followed by cavitation if the disease is not arrested. The early exudative lesion produces a soft shadow on the roentgen film; it is a rather soft, slightly dense, rather circumscribed area of varying size, while many grouped together constitute a large conglomerated shadow of the same character. The location of such chest shadows is of extreme importance. In the vast majority of cases, they will be found in the infraclavicular region or the apex of the lungs and well out toward the periphery, and in children, they are always accompanied by enlarged hilus lymph glands. Occasionally, this pathological change is located at the hilus and constitutes a typical hilus tuberculosis. Occasionally, the lesion may be primarily at the base, and such a lesion is extremely difficult to diagnose. Pleurisy frequently accompanies a chest infection due to tuberculosis, and most

cases of pleurisy with effusion of questionable etiology, particularly when there are repeated attacks, are due to this disease. Many times, no other signs in the chest can be elicited, either by physical or roentgen examination.

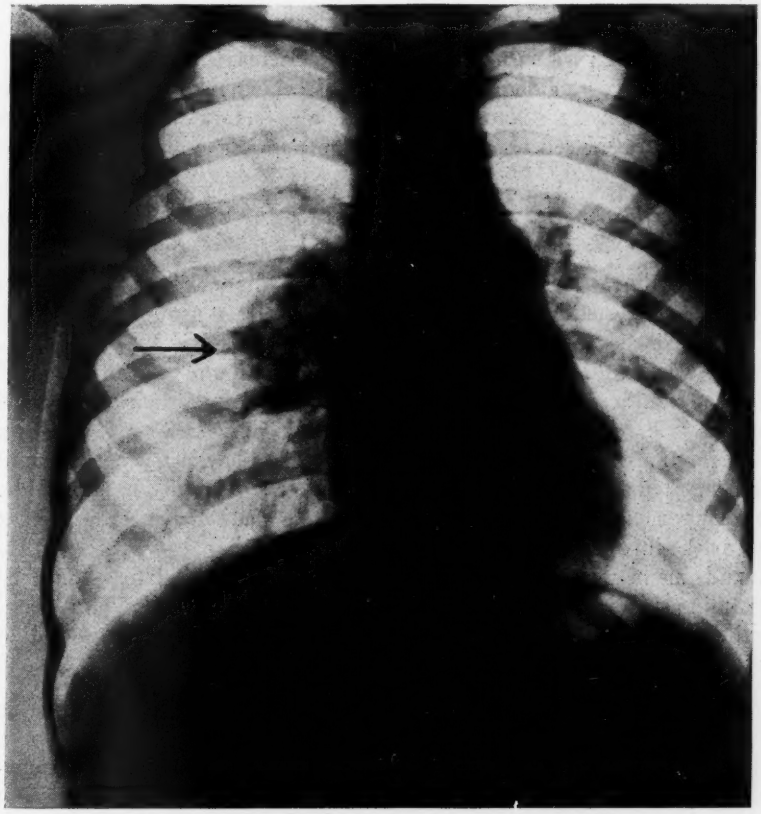

FIGURE 5.—Hilar pulmonary tuberculosis, glandular type.

Cavities may be well seen on roentgenograms of the chest and usually they have a thick, indurated wall and may contain some secretion. It is now a well established fact that so-called annular shadows seen on the roentgenogram are all evidence of a tuberculous process. A thickened pleura and the presence of fluid produces a homogenous shadow which is well visualized on the roentgenogram. It is essential that films be made of the mediastinum for the demonstration of mediastinal tuberculosis and enlarged glands. Allergy may result from tuberculosis,

producing a soft infiltration of the exudative type and giving the appearance of an extensive tuberculous lesion. This should always be considered as it will clear up very promptly in many cases and show only a small primary tuberculous area of involvement. This should not be mistaken for extensive healing of a pulmonary tuberculosis and cause the physician to curtail adequate rest and proper management of the patient. Likewise, large tuberculous glands and extensive fibrous infiltration, of which we will speak subsequently, may obstruct a bronchus and result in varying degrees of atelectasis, which also may be mistaken for an extension of the involvement. All these factors should be borne in mind and considered carefully before an opinion of the extent of the lesion is offered.

The roentgen appearance of various types of tuberculosis is shown in figures 1 to 7.

Tuberculin: The use of tuberculin in the diagnosis of tuberculosis was first suggested by Richard Koch and has been in use for forty years. This test is perhaps most valuable in children and if the reaction is positive in a child under five years of age, it should be considered of greater significance than in older children, although there are exceptions to this rule. The number of children with positive reactions varies in different localities—in rural areas sometimes as low as ten per cent and in congested areas, as high as forty per cent. If the reaction is positive, a roentgen examination of the chest should be made to ascertain whether an active involvement is present. If abnormal changes in the lung are found, members of the family, schoolmates, and associates should be examined, and further contact of the infected individual with normal children should be terminated. The disease may often be found in persons who present no symptoms whatever.

Blood Sedimentation Rate: This test has no definite diagnostic value in the presence of pulmonary tuberculosis, as it may be elevated in diseases other than tuberculosis, particularly in lesions of the inflammatory type. If a patient has a positive sputum, no further diagnostic test is necessary. The sedimentation rate is of value, however, in determining the activity of the lesion and may be helpful in giving information about the progress of the disease. If the rate becomes lower or normal, this information is helpful in governing the management of the patient.

Tuberculosis in Children

Autopsies usually show that there is involvement of the bronchial glands in nearly 100 per cent of all children less than one year of age who die from tuberculosis. The lungs are found to be involved in 97 per cent of cases. Therefore, it may be stated that tuberculosis in infants

involves (1) the right pretracheobronchial group, (2) the intertracheobronchial group, and (3) the peribronchial group. All these groups communicate freely among themselves and also with the lymphatics of the trachea, bronchi, lungs, and pleura, with the small subpleural glands, with the cervical gland chain, and with the sub- and supradiaphragmatic group. The lymph which passes through them ebbs and flows

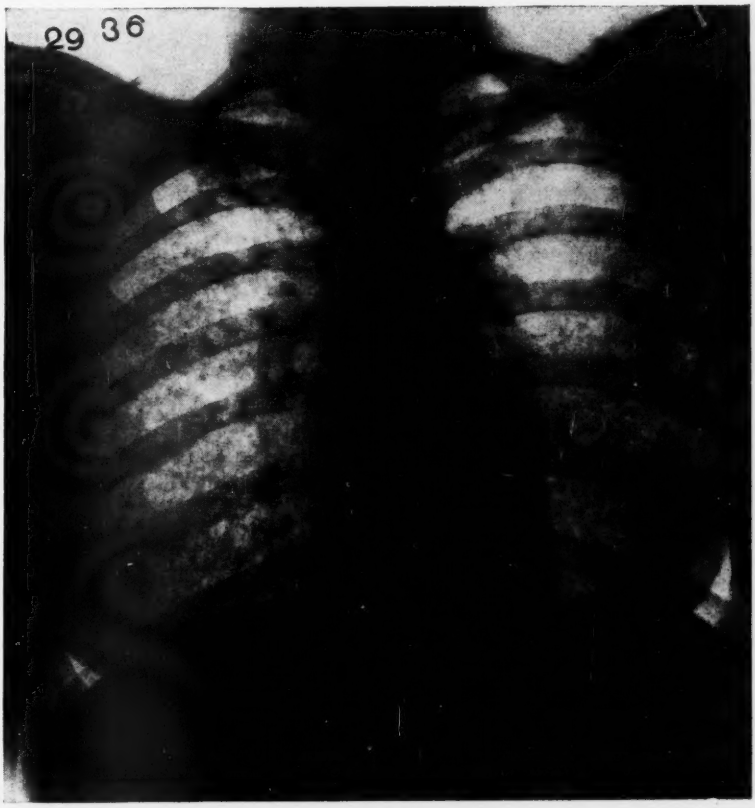

FIGURE 6.—Miliary pulmonary tuberculosis.

like a tide between the center and the periphery. Their whole principal mass, to repeat the simile of Weleminsky, is like a lymphatic heart, alternately dilated and contracted by the movements of the lung and the pulsations of the aortic arch.

In tuberculosis of childhood it is fair to assume that consequent to a tracheobronchial infection, whether of primary or secondary origin,

there almost always appears a more or less discrete or confluent eruption of tubercles in one or several of the innumerable lymph follicles in the zones of pulmonary parenchyma which are bathed by lymph—these are the so-called "Gohns." These in turn may go through the stages of repair and leave isolated calcific areas in the periphera, or may be entirely removed.

Chronic or Senile Tuberculosis

This disease is not uncommon in patients past sixty years of age and statistics derived from postmortem studies show it to be of frequent occurrence. It usually takes a particular form of chronicity which is often termed essential asthma, emphysema, or chronic bronchitis. The disease is insidious, tending to progress slowly, and the symptoms are mild. Care should be taken to rule it out in most of the chronic lung infections of advanced life, as many times these individuals are carriers of the disease. In all elderly individuals with a chronic cough, a roentgen examination of the chest and careful examination of the sputum should be made, as open cases of chronic tuberculosis are a great danger to the health of our population, particularly the unrecognized case.

Treatment

There have been many advances in the treatment of tuberculosis and it might be profitable to review a few of these. Rest in bed is perhaps the basic method of treatment as well as the oldest of all the remedial measures. It might be better to consider this as the first step in the management of a patient with pulmonary tuberculosis. In many patients with early manifestations, the disease will be arrested and cured by this method alone, and a small number of cavities may be spontaneously healed by such management. This treatment, however, is wholly inadequate for a large group of patients with pulmonary tuberculosis.

At the present time, artificial pneumothorax is probably the most useful procedure in addition to rest in bed. By this method, active lesions are compressed and the sputum is rendered free from bacteria. This not only expedites the cure of the patient, but also does much to prevent spread of the disease. Phrenic exeresis which is done either by resection of the phrenic nerve or crushing, puts the lung completely at rest and has produced very beneficial results in many cases. Both these methods of treatment are particularly applicable in unilaterial lesions as it is not usually practical to destroy both phrenic nerves or do a bilateral collapse. The use of a foreign substance such as an oil preparation known as oleothorax has been employed in the pneumothorax cavity. Large masses of paraffin have also been introduced to continue the compression and keep the lung collapsed permanently.

In the more advanced cases, thorocoplasty is sometimes resorted to. By this operation the ribs are removed on one side and the lung is completely and permanently collapsed.

Roentgenotherapy

The treatment of pulmonary tuberculosis by roentgenotherapy has not been successful in the usual type of pulmonary tuberculosis. How-

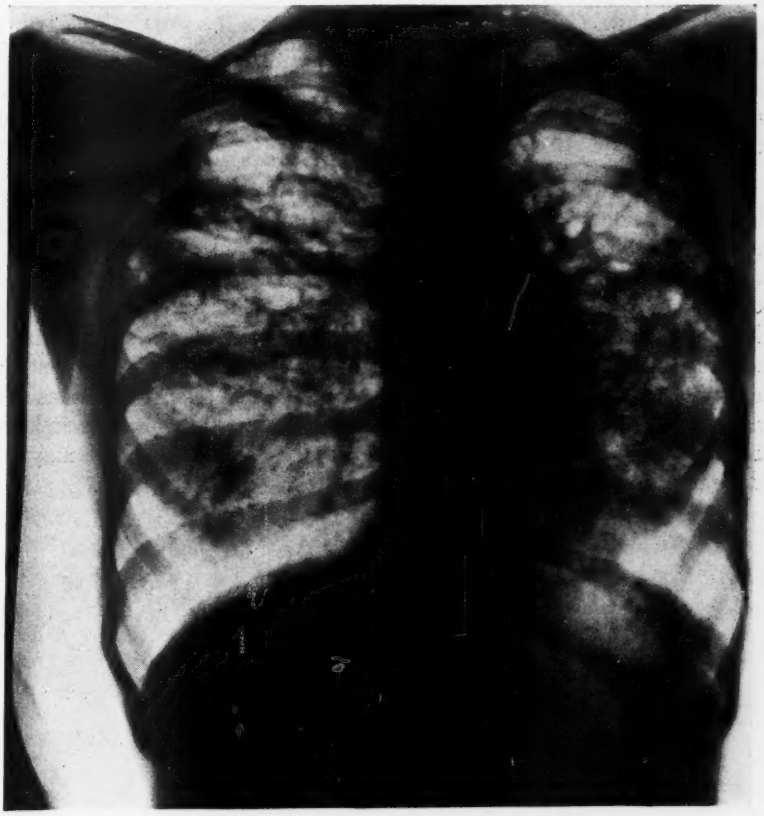

Figure 7.—Pulmonary tuberculosis, fibroid type.

ever, in tuberculosis of the hilus glands, particularly in children, we have secured splendid results in reduction of the glands and relief of the cough and other accompanying symptoms. This result is, we believe, akin to the treatment of tuberculous glands of the neck, a disease which has almost been eradicated by the elimination of tuberculous cattle from public milk supplies.

Climate: The question of the choice of a suitable climate always comes up in the treatment of tuberculosis. If we consider that the vast majority of cases of pulmonary tuberculosis occur in persons who live in congested areas—a penalty perhaps for our collective mass civilization—we could then believe that any area rather remote or isolated with an equitable climate would be most suitable; that is, a place more or less free from bacteria. This must be taken into consideration because, undoubtedly in most patients suffering from tuberculosis, a mixed infection sooner or later develops which probably accounts for the fatal termination in the majority of cases. Therefore, in many instances, patients under carefully supervised management may do well at home or in a well organized sanitarium irrespective of the climate.

In closing, we would like to emphasize the fact that the two most important factors in the diagnosis of both early and advanced pulmonary tuberculosis are the finding of pulmonary tubercle bacilli in the sputum or properly made and correctly interpreted, positive roentgenograms of the chest, or even more conclusive evidence is a combination of these. Many times, however, the sputum test has to be repeated a number of times before the organisms are found, while only a single roentgen examination is necessary. The physician should keep this disease in mind at all times and, if this is done and if individuals known to have been exposed to the infection are properly examined, much may be done to eliminate pulmonary tuberculosis.

THE SURGICAL TREATMENT OF ESSENTIAL HYPERTENSION

Report of Progress in 106 Cases

GEORGE CRILE, M.D.

My experience in the surgical treatment of hypertension began 23 years ago when I performed a unilateral adrenalectomy for this disease. The operation was followed by a temporary fall in the blood pressure which later rose again to the preoperative level. This partial, temporary success suggested adding to the unilateral adrenalectomy the partial resection of the other gland. The blood pressure was affected somewhat more than by the unilateral adrenalectomy alone, but it again rose to the disease level.

The adrenal glands, like the thyroid gland, are endowed with the power of compensatory hypertrophy but since the adrenal glands are essential to life, it is not safe to risk the onset of adrenal deficiency by extending the operation beyond a certain limit. If too much is excised, adrenal deficiency will follow; if too little is removed, restoration of the disease will follow. Therefore, a direct attack upon the adrenal gland would seem to be excluded. However, the marked effect of the removal of adrenal tissue in these early cases of hypertension indicated that the adrenal glands and the sympathetic system, when in a state of pathologic physiology, possess the power of affecting part if not all of the energy possessed by the muscles of the arterial tree from the aorta to the capillary bed. We, therefore, attempted to attack the function of the adrenal glands by denervating the glands in two seances. This procedure improved the effect upon the hypertension, the improvement or cure in some cases having lasted for as long as five years (Fig. 1.)

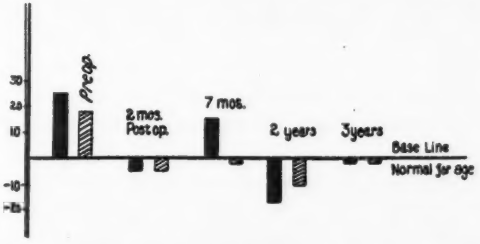

FIGURE 1: Chart showing the postoperative changes in the blood pressure in a patient with hypertension after adrenal denervation and division of the splanchnic nerves.

The cases in which these favorable results have been secured have included especially cases of hypertension in young subjects and cases

in which the hypertension has been associated with some disease also due to a pathologic physiology of the energy-controlling system such as hyperthyroidism, polyglandular disease, etc. But still recurrences occurred in too many cases. We, therefore, extended the operative procedure to include resection of the major, minor, and least splanchnic nerves. This operation improved both the immediate and the later clinical results. In view of the gravity of the disease we felt justified in recommending it, especially in view of the fact that headaches and other subjective symptoms were relieved. But it became evident that some other still undiscovered factor in the production of the hypertension must be found. We believed that this factor must be the effect of sympathetic stimulation of the nerves with which the entire arterial tree is so richly supplied; that is, in cases of hypertension the action of sympathin as well as that of the adrenal medulla extends to that part of the sympathetic system which supplies the energy of the arterial tree. The continued maintenance of the high blood pressure day and night with the constant reserve of energy at all times for crisis use indicates the presence of a generative mechanism of no small size and power.

At this point it occurred to us that clarifying evidence could be found by a study of the comparative anatomy and physiology of the energy systems of animals presenting evidences of wide variations in their equipment for the production of energy. The lion and the alligator may be cited as examples of the two extremes. If the ganglia of the sympathetic complex and the complex itself and the adrenal medulla are essential parts of a great power station, then in animals, the size of the adrenal medulla, the celiac ganglia, and the sympathetic complex should correspond with the power generated by each type of animal just as definitely as a motor corresponds with the function of the machine of which it forms a part—an aeroplane, a tractor, a low or a high-powered automobile, etc. Our research in Africa proved this conception beyond question.

Another significant observation indicates the function of the sympathetic system in the production and maintenance of high blood pressure. When, in the course of a denervation of the adrenal glands and division of the splanchnic nerves, the sympathetic nerves are manipulated there is a rise in the blood pressure, both systolic and diastolic, sometimes to such a height that it cannot be measured by a manometer, while on the other hand if the field is first flooded with novocain there is no rise but rather a dramatic fall in the blood pressure (Fig. 2). The adrenal-sympathetic complex is the only tissue in the body, the manipulation of which can thus specifically affect the blood pressure.

On the basis of these observations we resected the celiac ganglia, broke up the sympathetic complex, and denervated the aorta itself.

If we are right in our interpretation of the large body of facts supplied by our studies of comparative anatomy and physiology and by our clinical experience, we have in effect found a new organ which it would appear supplies the link that has been missing. The operative proce-

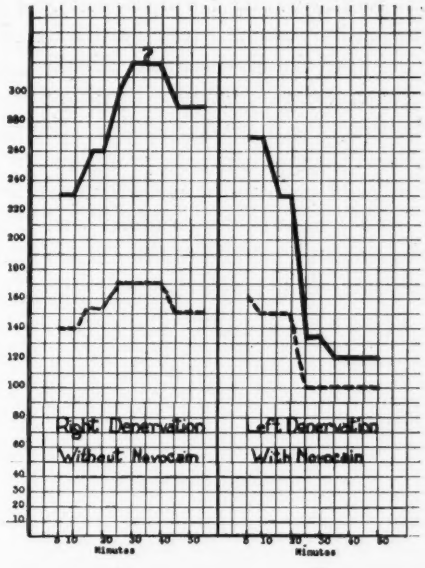

FIGURE 2: Chart showing the effect upon the blood pressure of manipulation of the sympathetic complex. (A) Without novocain and (B) after the operative field has been flooded with novocain.

dure based on these findings should enable us to reduce the high blood pressure of essential hypertension to normal on the operating table and since the post-ganglionic fibers cannot regenerate, there should follow a corresponding reduction in the blood pressure. There should be no disturbance of any other function, renal, bladder, gastro-intestinal, etc.; and, of considerable importance, the operative procedures can be completed in one seance.

Our experience with this new procedure now includes 25 cases, most of which were cases of malignant hypertension in an advanced stage. Our impressions from these 25 cases may be summarized as follows:

1. During the operation the blood pressure in cases of malignant hypertension is reduced to the normal level.

2. There is but a slight degree of shock as would be expected since the procedure is retroperitoneal.

3. The operation is performed in one seance.

4. Being in a painless area, nitrous-oxide oxygen provides ample anesthesia.

5. The clinical results during the operation and during the stay in the hospital show an improvement over those secured by our former procedures comparable to the effects of an adequate bilateral partial thyroidectomy as contrasted with those of ligation of the superior pole and unilateral lobectomy for hyperthyroidism. The present operation gives the impression of being a complete procedure, as during the stay in the hospital the blood pressure is more completely stabilized at a lower level than after the former operations, and there is a greater improvement in the eye grounds and in the kidney function as well as in the general well-being of the patient.

THE MANAGEMENT OF SYPHILIS IN ELDERLY PERSONS

E. W. Netherton, M.D.

Syphilis is one of the most serious of infectious diseases and each year late visceral lesions of the disease are responsible for the deaths of many individuals. Syphilis also has a high morbidity rate; consequently, the economic losses which are directly or indirectly traceable to this infection are appalling. This disease may simulate almost any condition and because of its protean manifestations, it is necessary that the physician should be familiar not only with its usual manifestations but that he should consider the possible presence of syphilis in the differential diagnosis of all chronic ailments. It has been estimated that approximately ten per cent of the adult population is infected with syphilis; therefore, every physician, whether he is a general practitioner or whether his practice is limited, is certain to be consulted by persons who present diagnostic and therapeutic problems caused by this disease.

Most syphilitics become infected in the second or third decade of life; therefore, the majority of elderly individuals who are now consulting the physician with symptoms and findings related to this infection contracted the disease before the arsphenamines and bismuth were used in treatment as extensively as they are now. Consequently, these individuals received little or no treatment in the early stages of their disease. Furthermore, the subsequent treatment which they received frequently was inadequate as compared with the present day standards of antisyphilitic therapy. Unless some means can be found to keep the young individual with acute syphilis under supervision long enough for the administration of adequate treatment, the practitioner will continue to see elderly patients for whom a decision of paramount importance must be made regarding the amount and type of antisyphilitic therapy which is indicated. The physician should not fail to explain to the young person with acute syphilis the necessity and importance of continuous and intensive treatment at this stage of the disease. The health and happiness of the patient and that of the future marital partner and their children as well as the removal of the patient's menace to the public health depends upon an intensive and judicious therapeutic attack in the early stages of the disease. The results obtained by modern antisyphilitic remedies leave much to be desired, but an early diagnosis followed by intensive and continuous treatment, as advocated by the Coöperative Clinic Group, will materially decrease the incapacitating and fatal affections of syphilis which occur in the fourth, fifth, and sixth decades of life.

After the acute manifestations of syphilis disappear, the disease becomes latent or asymptomatic. This relatively rapid disappearance of

the visible signs and subjective symptoms is somewhat unfortunate since this lack of evidence of the disease is responsible for the discontinuance of treatment by many infected individuals at this most inopportune time because they think it is unnecessary to submit to the inconvenience and expense which adequate antisyphilitic therapy entails. When a young person with acute syphilis fails to coöperate with his physician before an adequate course of treatment has been completed, he becomes a menace to others because of possible infectious mucocutaneous relapses, and the possibility that he will eventually obtain a serological or clinical cure is greatly decreased. In many such individuals, involvement of the cardiovascular and central nervous systems, or other types of late syphilis develop later, while other patients may reach the sixth or seventh decade of life with few if any clinical signs of the disease. It is with the latter group of patients that the physician must frequently decide what type of antisyphilitic therapy, if any, should be given.

A young person with a chancre or secondary syphilis seldom presents contraindications to intensive therapy; consequently, the treatment of acute syphilis can be fairly well systematized. The present day method of continuous treatment consisting of alternating courses of arsphenamine, bismuth, and mercury is well tolerated by young, vigorous individuals and insures better results than does the intermittent type of therapy which has been used in the past.

Patients with late syphilis and especially those who have had a syphilitic infection for several years should not be subjected to a systematized type of treatment such as is used in acute syphilis. This fact was not so well established during the earlier period of the use of arsphenamine therapy; consequently, intensive and more or less systematized treatment which was administered to individuals with late syphilis frequently produced disastrous results. It is now known that many of these untoward results of arsphenamine therapy were due to the injudicious use of the drug rather than to its impurities or its toxic effect. Experience has clearly demonstrated that the treatment of late syphilis must be individualized rather than systematized. With this view in mind, what type of treatment should be administered to a syphilitic patient who is past sixty years of age? Obviously, the duration of the disease, the physical condition of the patient, and the amount and type of past treatment which the patient has received are more important factors than the age. The serious late manifestations of this disease which often involve the cardiovascular and central nervous systems manifest themselves most frequently between the ages of thirty-five and fifty and require a more complicated and individualized type of treatment than is necessary for some other types of late syphilis.

THE MANAGEMENT OF SYPHILIS IN ELDERLY PERSONS

Acute Syphilis in Elderly Persons

Although syphilis, when seen in elderly persons, usually is in a late stage, an acute infection occasionally occurs. The acute manifestations do not differ from those seen in younger individuals. Because of the age of the patient, extragenital lesions, particularly those occurring on the lip, may be confused with malignancy; likewise any resistant, inflammatory lesion which develops around the nail fold and is associated with adenitis which occurs early should be suspected of being a chancre. This should be considered especially in the case of physicians who might become infected while doing obstetrical work. Such errors in diagnosis can easily occur when the physician fails to note carefully the characteristics of the lesion. A chancre is an infiltrated, inflammatory lesion which has been present for a comparatively short time. If it is seen early and before topical applications have been used, it will usually have a superficial, clear cut erosion at the center from which a serous exudate can readily be obtained. It does not bleed as easily as a carcinoma, and it is accompanied by a more rapid enlargement of the regional lymph nodes. Other manifestations of acute syphilis such as general malaise, headache, generalized body pains, and lesions of the skin and mucous membranes, if present, aid in clarifying the differential diagnosis. In all questionable lesions, a dark-field examination should be made. If the lesion has been present as long as three weeks, a Wassermann test is of value but the serological findings must, as at all times, be interpreted with due consideration of the clinical findings.

The treatment of acute syphilis in elderly patients is similar to that in youth. It should be as intensive as the physical condition of the patient will permit. Age alone is not a contraindication to adequate treatment in such cases; however, mercury should not be given and courses of the arsenicals should be modified if the patient has impaired kidney function. Hypertension does not necessarily contraindicate the use of the active spirocheticidal arsenicals in the treatment of acute syphilis.

The physician hopes to obtain a twofold objective by his treatment: (1) to eradicate the infection to the extent of accomplishing what is at present considered to be a clinical and serological cure, and (2) to prevent further spread of the disease by quickly and permanently removing all infectious lesions. It is very important that these objectives be attained in young individuals for they have a long life expectancy during which the occurrence of late visceral involvement would be disastrous. Likewise, they are at the age of sexual activity, and if adequate treatment has not been administered, they may infect others. The necessity of obtaining a cure in an elderly person with acute syphilis is not so

important as it is unlikely that they will live long enough for the serious late manifestations of the disease to develop; however, treatment should be sufficiently intensive to insure against the development of infectious relapses.

The treatment of acute syphilis in elderly persons should be continuous for at least a year and should consist of alternating courses of neoarsphenamine and bismuth such as is used in acute syphilis in younger individuals. Mercury should not be used because of its damage to the kidneys. It is possible that mapharsen will be the arsenical of choice for elderly patients because of the relatively few complications and reactions which have been observed following its administration. However, further observation is necessary before the comparative value of this new arsenical can be established.

Late Syphilis in Elderly Persons

A few syphilitics who have received little or no treatment during the early stages of their disease will reach the age of sixty or more with very little if any clinical evidence of their disease, while others will present signs which are compatible with the diagnosis of late syphilis. In some cases the signs are the results of scarring and are not always proof of the presence of marked activity of the disease. For example, an elderly syphilitic may have fixed pupils, absent reflexes, or a scarred smooth tongue with areas of leukoplakia on its surface, all of which may be sequelae of the inflammatory reaction of late syphilis and at times it may be very difficult to evaluate these findings properly. However, a careful history of the patient's complaints and of the type and amount of past treatment is of great value and should be considered carefully and correlated with the physical and laboratory findings before the final disposition of each case is made. Other patients may present definite manifestations of late syphilis such as nodular ulcerative syphilids, or a gumma of the nasopharynx.

A positive Wassermann reaction does not necessarily mean that a lesion is due to syphilis nor does a negative reaction rule out syphilis as a diagnosis. In spite of this, the test should be included in a thorough examination of every patient and the serologic findings must be correlated with the clinical findings. It is important to keep in mind that the reaction is apt to be negative in the presence of late syphilis.

The first prerequisite in the management of syphilis of many years' duration is a careful physical examination. Special care should be exercised in evaluating the condition of the myocardium and the coronary circulation, and, if possible, the physician should decide what part if any the syphilitic infection plays in the production of the patients' symptoms. If a patient is past sixty years of age and if the only evi-

dence of syphilis is a positive Wassermann reaction, there is little likelihood that serious late manifestations of the disease will develop; in all probability, he will live out his life expectancy and die from some other cause. This type of patient cannot be cured of his syphilis, and he will not transfer his infection to others; therefore, antisyphilitic treatment should be withheld as much harm may result from too intensive treatment. A mild treatment consisting of potassium iodide and mercury by mouth in the form of mixed treatment tablets or in compound syrup of sarsaparilla seems to benefit some elderly syphilitics. The formula for this is:

Bichloride of mercury	gr. I. or gr. II.
Potassium Iodide	drams IV
Com. Syrup Sarsaparilla	oz. IV

A teaspoonful of the mixture should be taken after each meal at varying periods of two months at a time. The use of arsenicals is definitely contraindicated in this type of case.

In cases in which late manifestations of the disease are present or in which there is reason to believe that the syphilitic infection is responsible for the patient's symptoms, conservative antisyphilitic therapy should be administered. Individualization of treatment is very essential in this type of patient. It is important that an accurate evaluation of the condition of the vital viscera be made before treatment is started. The type and amount of treatment should be planned so as to avoid the two most common disasters which may result from too intensive treatment of late syphilis. These are (1) therapeutic shock or the Herxheimer reaction, and (2) therapeutic paradox. The Herxheimer reaction refers to the inflammatory reaction which sometimes occurs at the site of a syphilitic process a few hours following the administration of active spirocheticidal remedies, particularly the arsenicals. Such a reaction may be disastrous when it occurs at vulnerable spots such as the orifices of the coronary arteries. Because of this, the rapidly acting spirocheticidal drugs should never be used as the initial treatment of late syphilis and this is particularly true in elderly individuals. The therapeutic paradox refers to the disastrous results which occur when the healing of a syphilitic focus occurs too rapidly to permit physiologic compensation of the involved organ. This unfortunate result of treatment occurs mainly in cases of late hepatic and cardiovascular syphilis. Like the Herxheimer reaction, the therapeutic paradox occurs most frequently following the administration of the arsenicals.

These disastrous results of antisyphilitic therapy can be avoided by the use of slowly acting remedies such as bismuth and mercury. Bismuth is the drug of choice for the elderly syphilitic with late manifestations which require treatment. Some authors have observed a mild

Herxheimer reaction following the administration of bismuth but such an experience is very uncommon and, if the first four doses are less than is usually administered, there is little to fear from its use. Another advantage in the use of bismuth is that it does not impair kidney function as much as mercury. An insoluble salt such as bismuth salicylate will be absorbed slower than the soluble preparations and is to be preferred when slow healing is desired. Potassium iodide in gradually increasing dosage to the point of tolerance is an important part of the treatment of late syphilis and is especially valuable in elderly patients.

Weekly injections of bismuth and the oral administration of potassium iodide will be sufficient treatment for the average elderly patient with late syphilis. Potassium iodide in as large amounts as are well tolerated should be given during the course of bismuth. A course of fifteen or twenty injections is usually well tolerated. Courses of treatment alternating with a rest period of two months should be given until the maximum benefit which may be expected has been obtained. The patient should be examined periodically, and the subsequent treatment should depend upon the progress of the disease. A course of twelve injections of bismuth each year and the administration of potassium iodide at regular intervals each year are well tolerated and will help keep the disease arrested.

Arsenical therapy should be given only in cases in which the syphilitic lesion has not disappeared or the progress of the disease has not been arrested by potassium iodide and bismuth. Treatment should never be started with an arsenical. Arsphenamine should not be used in elderly people. Neoarsphenamine is the arsenical of choice; the initial doses should be small and the maximum dose should not exceed 0.45 gm. Bismarsen may be used instead of neoarsphenamine; however, the initial doses should be small and the patient should be given the preparatory treatment with bismuth and iodides before the administration of this drug.

Summary

The treatment of acute syphilis in elderly people is similar to that used in acute syphilis in young individuals. In elderly patients, it is not so important that the object of treatment should be to produce a clinical and serological cure because the life expectancy is not great enough to allow for the development of the late, serious manifestations of the disease. However, the treatment should be continuous for at least one year, during which time arsenicals and bismuth are alternated. If well tolerated, the treatment should be continued for another six months. It is important, however, that the treatment be sufficiently intensive to insure against recurrences of infectious lesions in order to prevent further spread of infection.

THE MANAGEMENT OF SYPHILIS IN ELDERLY PERSONS

Treatment of late syphilis in elderly persons must be individualized. Before treatment is started, the patient should be examined carefully to determine whether there is any involvement of the vital viscera which might be activated by antisyphilitic therapy. The treatment should be intensive enough to arrest the progress of the disease only, and no attempt should be made to eradicate the infection. It is only by conservative treatment, which is adapted to each individual case, that the patient has a chance of living out his life expectancy. If this is not kept in mind and if treatment is intensified, much harm may be done. This is especially true if the arsenicals are used before the patient has received thorough preparatory treatment with iodides and bismuth.

Elderly patients who are in comparatively good health yet have positive serologic findings and few or doubtful clinical signs of an old syphilitic infection should be treated only if signs which may be considered to be due to the infection develop. It is this type of patient in whom mixed treatment by mouth is sometimes beneficial.

A REVIEW OF PERIPHERAL VASCULAR DISEASE*

JOHN TUCKER, M. D.

GENERAL CONSIDERATIONS

The modern conception of peripheral vascular disease has been clarified to a considerable degree during the past decade by a better understanding of the physiology of the arterioles and capillaries. Hundreds of articles have been published by various investigators who have made intensive studies of the peripheral circulation in animals and in man. As the result of this work, a much better classification has been evolved, which is based on special diagnostic tests and on the results of medical and surgical therapy.

The picture of peripheral vascular disease is very complicated. While the most frequently encountered conditions are Buerger's disease, arteriosclerosis, embolism and thrombosis, Raynaud's disease, erythromelalgia, and acrocyanosis, many other morbid changes may occur in the peripheral circulation and these merit thoughtful attention.

How shall we attack this problem? It is evident that the first consideration must deal with the patient as a whole. Is he well nourished or does he suffer from malnutrition and deficiency disease? Does he have arterial hypertension or hypotension, arteriosclerosis or diabetes? Is he suffering from rheumatic, syphilitic, or arteriosclerotic heart disease? Does he carry executive responsibilities? What are his habits of living? Is he intemperate in the use of alcohol and tobacco? These and many other questions must be settled by means of a painstaking history, physical examination, and laboratory tests. Our first approach, then, must consist of a careful survey of the patient as a whole. This procedure alone will, in many instances, suggest the type of peripheral vascular disease which is producing the symptoms.

We have, as yet, no satisfactory diagnostic criteria for vascular lesions of the viscera except for the heart itself; however, the circulation of the extremities is quite available for interpretive study.

It is necessary to make a few comments in regard to the physiology of the peripheral vessels. The fluctuation in the peripheral tone of these vessels of the extremities varies with the external temperature, the internal heat of the body, and the emotions. Sir Thomas Lewis[1] describes the reaction to cold as first vasoconstriction followed by vasodilatation, the so-called "axon reflex." In the control of the body temperature, the skin dissipates 76 per cent

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of the total heat by convection and radiation, while 24 per cent occurs through vaporization of sweat and through loss of water vapor from the lungs. During hard labor, however, most of the heat loss is brought about by vaporization of sweat. The extremities, which comprise about 65 per cent of the body surface and which contain no vital organs, are important structures for heat regulation. This function requires a very delicate vascular control, especially since the arms and legs are exposed much more to sudden changes in temperature than other parts of the body with the exception of the face.

Krogh[2] has shown that the arterioles and capillaries are sensitive to hormonal influences; however, for our purpose, we will accept the hypothesis that the major control is through the sympathetic nervous system. These vasomotor nerves, when activated, cause constriction of the arterioles. There is no conclusive evidence to prove that vasodilator nerves exist in man.

The postganglionic fibers of the sympathetic nervous system accompany the spinal nerves and supply the blood vessels, sweat glands, and pilomotor muscles of the periphery. This fact is easily demonstrated, for if we cut the ulnar nerve, for example, there results not only anesthesia in the skin supplied by this nerve but also a loss in vascular tone.

The diseases which affect the extremities are many and varied; however, our ability to properly classify these abnormal states depends on the diagnostic methods that we use.

Diagnostic Measures

In this discussion we wish to stress particularly those procedures which are not only simple in nature but also those which can be used by the physician at the bedside without special instruments of precision.

A. Inspection of the Extremities

1. Pallor is present when the superficial blood vessels are empty or only partially filled. If it becomes more marked when the extremity is elevated slightly above the level of the heart, there is probably structural impairment of the circulation. If the pallor is associated with coldness, there is deficient arterial flow. This becomes still more evident if cyanosis develops when the limb is placed below the horizontal level.

2. Redness indicates a superficial dilatation of the capillaries. If the rubor is cold, there is capillary stasis associated with diminished inflow of blood. If the skin is red and warm, there is increased minute volume flow through the capillaries.

3. Cyanosis is produced by an insufficient supply of oxygen in the vessels of the skin. When the cyanosis fails to disappear with the local application of heat to the limb, as with an infra red lamp, there is probably organic obstruction of the arterioles.

4. Ulceration, when chronic and indolent, is produced by impaired arterial flow plus infection.

5. Gangrene in the extremity is the result of a prolonged impairment in the arterial blood supply.

B. Observation of Postural Changes in the Extremities

1. Deepening cyanosis in a dependent limb is produced by stasis in toneless superficial vessels.

2. Rubor on dependence of the limb indicates dilatation of the vessels of the skin. This is often due to local injury of the capillaries.

3. Rubor and cyanosis on dependence of the limb indicate that there is dilatation of the capillaries plus marked impairment in the minute volume flow of blood through the affected extremity.

C. Palpation of Blood Vessels in the Extremities

Usually one can feel pulsation in the normal arteries when the body and limbs are warm. However, this is modified considerably by the amount and character of the tissues which surround the artery and also by the location of these vessels which may, in certain instances, take an unusual course. While a good pulsation may be felt in the larger artery, the spasm or obstruction may be more distally placed in the arterioles or capillaries. On the other hand, absent pulsation may not be inconsistent with adequate capillary circulation. Reich[3] has shown that, in normal people, the dorsalis pedis pulsation is absent in 4 per cent and abnormally placed in 8 per cent, while the posterior tibial pulsation is absent in 5 per cent. We should not rely too greatly on the significance or absence of pulsation in the pedal arteries. As a routine measure, however, we should feel for the pulsation in all palpable arteries including the digital, radial, brachial, axillary, dorsalis pedis, posterior tibial, popliteal, and femoral.

The simple methods of palpation and inspection, when correlated with the general condition of the patient, will, in the majority of cases, tell us all we need to know about the dynamics of the peripheral circulation.

In certain instances, however, it may be necessary to employ more elaborate diagnostic procedures. These include:

1. Surface temperature readings by the electric thermocouple. By this method the gradient of temperature change is determined at various points from the proximal to the distal portions of the extremity. This is compared with the readings on the normal side. Any sudden decrease in the temperature indicates an impairment in the circulation.

2. Oscillometry, as employed by the Pachon oscillometer, gives the pulsation of the sum total of the arteries in the limb.

3. Reaction to histamine is employed especially to determine the optimum level for amputation. It indicates the available flow of blood into the skin and gives some idea of the efficiency of the collateral circulation. The method used is to maintain the limb in a horizontal position at room temperature. The histamine, 0.1 cc. of 1:1000 solution, is injected intracutaneously. The wheal and flare should appear within five minutes and manifest a certain redness and size. This procedure has certain value when compared with other diagnostic measures.

D. Differentiation of Structural Disease from Vasospastic Disorders

From a therapeutic standpoint, we are able, in most cases, to differentiate structural disease from vasospastic disorders; also we can evaluate the degree of vasospasm and the probable success of sympathectomy. This requires a period of observation in the hospital for a week or more.

1. The most satisfactory test is the determination of the effect on the peripheral circulation of an increase of the internal production of heat. Normally, there is vasodilatation of the arterioles of the extremities when the temperature of the body is elevated above the normal range. The use of a hot tub bath, rubber blanket, heat cabinet, or typhoid shock are all valuable in selected cases. It is best to estimate change in the peripheral temperature by use of the electric thermocouple. Readings on the sound and affected limb are compared to determine the degree of change. It is obvious that this method should not be used in aged and debilitated patients or in those individuals who have cardiovascular renal disease.

2. A second important method of study is to block the sympathetic pathways to the peripheral vessels. This can be brought about in the lower limbs by spinal anesthesia and peripheral nerve block. Similar effects can be obtained in all four extremities by the use of general anesthesia. Details of the technique are available in the publications of Morton and Scott[4].

3. In a few cases where the site of vascular obstruction is still obscure, information of value can be obtained by arteriography. When thorium dioxide is injected into the arteries proximal to the region of impaired circulation and roentgenograms of the affected extremity are made, details of the arterial and capillary circulation can be visualized. This method may serve to differentiate between thrombo-angiitis obliterans and arteriosclerosis. In the former there is often increased capillary circulation while in the latter, the anastomotic channels are limited in number. Considerable experience is required to interpret the roentgenograms.

The recognized diseases of the peripheral vascular system may be divided into organic and vasospastic. The principal points of diagnostic importance in those diseases which we commonly see in our daily practice are noted below.

Organic Lesions

A. Thrombo-angiitis obliterans

1. A disease of active maturity.
2. More common in men.
3. Most frequently observed in Hebrews.
4. Commonly associated with the excessive use of tobacco.
5. Pallor of extremity when elevated 90 to 180 degrees.
6. Flushing of the dependent limb.
7. Diminished pulsation in the arteries of the feet.
8. Pallor of foot on passive motion.
9. Migrating phlebitis in from 20 to 25 per cent of cases.
10. Associated scleroderma (occasionally).
11. Trophic changes, i.e., superficial blebs, desquamation.
12. Arteries seldom visualized by plain roentgenograms.
13. Increased collateral circulation by arteriography.

B. Arteriosclerotic gangrene

1. Cardiac hypertrophy, hypertension, palpable thickening of arteries, accentuated aortic second sound.
2. Arteriosclerosis of fundus and conjunctival vessels.
3. Calcification of larger arteries—demonstrated by roentgenograms.
4. Absence of arterial pulsations in feet (not diagnostic).
5. Coldness of extremity.
6. Pallor and cyanosis of limb.
7. Coldness.
8. Gangrene—trauma plus infection.

Symptoms Suggestive but Not Diagnostic of Arteriosclerotic Gangrene

1. Increasing intolerance of extremities to cold.
2. Acroparesthesia.
3. Muscular fatigue.

4. Aching pains.
5. Nocturnal cramps and hot feet.
6. Intermittent claudication.

C. Arterial Embolism

PREDISPOSING FACTORS

1. Rheumatic heart disease.
2. Bacterial endocarditis.
3. Auricular fibrillation.
4. Mural thrombi after coronary occlusion.

SYMPTOMS

1. Extreme pain at site of embolus, one and two hours after obstruction of vessel. Pain spreads peripherally.
2. Local waxy pallor.
3. Dark blue cyanosis distally.
4. Proximal blotchy discoloration.
5. Coldness distally.
6. Decreased cutaneous sensibility.
7. Reduced reflexes in affected limb.
8. Paralysis in certain cases.
9. Gangrene if collateral circulation is deficient.

D. Latent Phlebitis

This condition, which is very common, may follow local trauma, burns, local and focal infections. It is bacterial in origin.

SYMPTOMS

1. Aching and pains in the extremities involved.
2. Early fatigue of affected parts.
3. Cramps in muscles.
4. Sense of undue heat.
5. Local itching and eczema.
6. Deep veins sensitive to pressure.
7. Variations of symptoms with barometric pressure changes.

Other conditions which are encountered less commonly are venous thrombosis in the axillary vein induced by effort, periarteritis nodosa, and specific and nonspecific arteritis.

FUNCTIONAL VASOSPASTIC DISEASES

A. Raynaud's Disease

STAGES

1. Arterial spasm, white syncope, local asphyxia.
2. Capillary dilatation (reflex—cyanotic asphyxial stage).
3. Arterial relaxation—warm red stage.

DIAGNOSTIC CRITERIA (Allen and Brown[5]).

1. Intermittent attacks of discoloration of distal parts.
2. Symmetrical bilateral involvement.

3. Absence of clinical evidence for occlusive disease of the peripheral arteries.
4. Gangrene and trophic changes limited largely to the skin; may be associated with scleroderma.
5. Absence of primary organic disease.
6. Predilection for women.

B. Erythromelalgia (Weir Mitchell's Disease)

CHARACTERISTIC FEATURES

1. Bilateral burning pains, often in intermittent attacks.
2. Sudden increase in redness, flushing or congestion, and increase in temperature of dependent limb.
3. Production and aggravation of the distress by heat and exercise.
4. Relief of discomfort by means of rest, elevation, or the application of cold to the affected extremity.
5. Bilateral distribution of the disease.

C. Acrocyanosis

This condition occurs quite commonly in young people—often at puberty—and in those who have an unstable sympathetic nervous system. There may be associated symptoms of an endocrine disturbance. It is often a part of the syndrome of neurocirculatory asthenia. There is sweating and coldness of the hands and feet; the sweating is profuse and some puffing occurs in the affected areas. The symptoms are increased by exposure to cold or by psychic stimulations.

Secondary vascular spasms may occur in a variety of different conditions which produce sympathetic irritation. These include:

1. Neurological conditions, such as poliomyelitis, multiple sclerosis, amyotrophic lateral sclerosis, syringomyelia, hemiplegia in late stages, and spina bifida.
2. After trauma such as strains, contusions, and fractures.
3. In certain cases of cervical rib.
4. Following the prolonged use of a pneumatic hammer. As a rule, such vascular disturbances are not difficult to diagnose if we will but think of all the possibilities in each case.

TREATMENT

The treatment of peripheral vascular disease is brought up to date in the very excellent review by Scupham and De Takáts[6]. In this comprehensive article, the therapy is divided into medical and surgical procedures. The former include specific and general measures, the use of drugs, biological products, and passive vascular exercise. The surgical measures include efforts to improve impaired circulation, to alleviate pain, and to remove nonviable parts at an optimal time and at an optimal level. We can only offer a summary of those measures which are of a practical value. Further details will be found in the original article.

Medical Therapy

A. Specific measures

1. If polycythemia vera is the underlying cause, acetylphenylhydrazine or x-ray therapy may be used.
2. In associated hypothyroidism, the proper dose of thyroid extract is necessary.
3. Syphilis requires adequate antiluetic therapy.
4. Congestive heart failure necessitates rest, digitalis, and often mercurial diuretics.

B. Foci of infection

1. Acute and chronic foci of infection must be eliminated by the use of proper measures.

C. Measures to avoid amputation of the affected arm or leg

1. Keep the entire body warm.
2. Protect the feet from trauma, chilling, and infections.
3. Use the temperature foot cradle (optimum temperature for the relief of pain is 33—35°C.)
4. Use contrast baths.
5. Keep the position of the limb at the level of greatest circulatory efficiency, usually 10—15° below the horizontal position.

D. General measures

1. Bed rest.
2. *Prohibit all use of tobacco* in all instances of peripheral vascular disease.
3. Artificial fever (typhoid), especially in Buerger's disease.
4. Intravenous saline solution, 5 per cent, in mild cases of Buerger's disease.

E. Tissue extracts intramuscularly may be tried for the relief of intermittent claudication. Insulin-free pancreatic extracts are best, but extracts of skeletal muscle have been used. Apparently, as the result of such injections, there is increased ability of the muscles to do work with the available blood supply. Many patients do well with one injection a week.

F. Drugs

1. Alcohol, in doses of 0.5 cc. per kilogram of body weight, produces vasodilatation in short periods. It is valuable in arteriosclerosis with occlusion for relief of pain, and it may reduce the severity of a chill after the use of intravenous typhoid therapy.
2. Theobromine compounds are of value in aiding prolonged vasodilatation, especially in arteriosclerosis. Theophylline ethylenediamine produces similar effects.
3. Papaverine has been employed in sudden arterial occlusion (Denk). It is given intravenously every two or three hours if necessary for several days. It should relieve the symptoms after two injections, if at all. Apparently, the benefit is due to relief of widespread arterial spasm.

G. Passive vascular exercise (Pavex)

Alternate positive and negative pressure is applied to an extremity.

1. Landis and Gibbon[7] employ an aluminum box with the extremity sealed in a rubber cup. Suction is used at 120 mm. of mercury for 25 seconds and pressure is maintained at 80 mm. of mercury for 5 seconds.

2. Hermann and Reid[8] have devised a glass boot. In this, suction is limited to 80 mm. of mercury and pressure to 20 mm. of mercury. If the response is satisfactory, a rise in cutaneous temperature appears in all patients who are treated two weeks or more. All evidence of pain disappeared in 86 per cent of the patients, and the pain of ischemia has been gradually relieved except in severe gangrene. Small changes of pressure should be used at first, and acute infection and venous thrombosis are a contraindication for this therapy. The results are most satisfactory in cases where only the smaller vessels are involved.

Surgical Therapy

More recently, there has been a conservative attitude toward surgical treatment. This is largely due to: (1) the earlier recognition of disease of the peripheral circulation; (2) a more thorough understanding of etiology; and (3) a better understanding of natural methods of compensation for circulatory disorders.

Three surgical procedures are in use which are designed:

A. To improve impaired circulation

1. Ligation of a vein has been used especially in arteriosclerosis and thrombo-angiitis obliterans. There is no sound physiological basis for this procedure. Better results have been observed in acute rather than in chronic obstruction. When favorable results occur, there is increased systolic pressure, increased venous pressure, diminished volume flow of blood, increased surface and deep temperature, increased collateral circulating bed, and the diminished incidence of gangrene. However, in most cases there is no definite or proven benefit.

2. Arterial ligation may be done to stimulate collateral circulation, especially in Buerger's disease. As a rule it is not successful.

3. Arterial excision (arteriectomy) is presumed to interrupt reflex vasoconstriction. This also is not entirely successful.

4. Periarterial sympathectomy (Leriche) consists in the removal of sympathetic nerve fibers from the veins and main nutrient artery. The hyperemia which results appears to be evanescent.

5. Sympathetic ramisection consists of interruption of the gray rami connecting the ganglionated trunk with the peripheral nerves. Objections to this procedure are that: (1) it is difficult to distinguish all anatomic variations, and (2) the posterior ganglion fibers readily regenerate.

6. Sympathetic ganglionectomy is preferred. In the upper extremity it is necessary to cut the dorsal sympathetic trunks below the second dorsal ganglion. For the lower extremity, the second, third, and fourth lumbar ganglia must be removed.

B. To alleviate pain

1. Peripheral nerve block by use of alcohol, sectioning, and crushing.
2. Paravertebral block which is used in elderly patients.
3. Intraspinal injection of alcohol.
4. Chordotomy (spino-thalamic tracts).

C. To remove nonviable parts, especially in arteriosclerosis and diabetic gangrene.

The site of amputation is determined by the skin temperature and the reaction to histamine. These usually indicate the same level of circulatory efficiency.

Conclusions

1. The proper diagnosis of peripheral vascular disease requires consideration of the general condition of the patient and his age, sex, and race, as well as the use of one or more of the diagnostic measures outlined above.

2. Treatment should be conservative. Medical measures should be used if possible or surgical treatment may be instituted to improve local circulation, to alleviate pain, and to remove devitalized parts.

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TYPES OF ARTERIAL HYPERTENSION AND THEIR RECOGNITION

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Although the most common cause of a consistent elevation in blood pressure is essential hypertension, there are a number of other pathologic states which are regularly attended by increased arterial pressure. Certain of these states are an established part of general medical knowledge; others are decidedly unusual, and one has been set aside as a distinct clinical entity only within recent years. Needless to say, it is of considerable importance that the hypertension of all these conditions be differentiated from the common type of elevated blood pressure. Fortunately, differential diagnosis usually is a simple matter, although in certain instances it may be impossible to arrive at a definite conclusion even after the most detailed clinical and laboratory studies. It will be our purpose in this communication to review the various causes of hypertension with particular reference to those features which are of value in distinguishing one type from another.

ESSENTIAL HYPERTENSION

Essential hypertension is characterized by a continuous, though often variable, elevation of blood pressure in the absence of glomerulonephritis and other conditions known to cause increased arterial tension. The term must still be interpreted to indicate a symptom complex rather than a disease entity, and it is probable that as medical knowledge increases, distinct types of cases will be separated from the main group on the basis of specific etiologic factors. In essential hypertension both the systolic and diastolic blood pressure are increased. Tests of renal function, in the early stages, give normal results, but as time passes, a progressive diminution in function frequently is recorded, and a certain number of patients, probably not more than 10 per cent of the entire group, ultimately die of uremia. Cardiac complications, such as congestive heart failure and coronary artery disease, are of much greater clinical importance and are the cause of death in approximately 60 per cent of all patients, while cerebral vascular accidents constitute the terminal event in 15 or 20 per cent of the cases.

Although the actual cause or causes of essential hypertension remain unknown, there is general agreement that the elevation in arterial pressure is due to increased resistance in the peripheral circulation. Recent studies[1] indicate that both in this type of hypertension and in the hypertension resulting from glomerulonephritis, the augmented resistance is present in all parts of the systemic circulation and is due to an

intrinsic increase in the tonus of the blood vessels and not to organic changes in the vessel walls or excessive vasomotor stimulation.

Essential hypertension may be divided into three types, the benign, intermediate, and malignant, according to differences in the ophthalmoscopic findings. In the benign form, sclerosis of the retinal arteries of variable degree is observed without other abnormal changes. The malignant type, on the other hand, is characterized by the presence of neuroretinitis with edema of the optic disk and surrounding retina. The edema frequently is out of proportion to the other retinal changes, such as hemorrhagic areas, cotton-wool exudates and arteriosclerosis. Differentiation of typical cases of benign and malignant hypertension is comparatively simple, but there is a group of cases which cannot be placed in either of these classes. Ophthalmoscopic examination reveals more extensive changes, in the form of exudates and hemorrhagic areas, than are present in patients with benign hypertension, and yet, because of the absence of papilledema, the condition cannot be classified as malignant hypertension. These cases are therefore placed in the intermediate group. Even in the malignant group, renal function frequently is normal or only slightly reduced at the time the condition is first recognized, and the erythrocyte count and hemoglobin content of the blood are seldom more than slightly diminished until after the development of renal insufficiency. Although the malignant and intermediate forms of essential hypertension usually develop upon earlier hypertension of the benign type, the majority of patients with benign hypertension run the full course of the disease to a fatal termination without progressing to the intermediate or malignant stages. The characteristic pathologic feature of the malignant and intermediate types consists of widespread hypertrophy of the media and proliferation of the intima of the arterioles[2, 3]. These changes have been observed in practically all the organs and tissues of the body, and they are usually absent in the benign form of hypertension. In view of the observations of Prinzmetal and Wilson[1], however, the progression from benign hypertension to the more severe types cannot be attributed to the development of these pathologic changes. There is, on the other hand, considerable evidence to support the view that the change to the malignant type is due to greatly increased, generalized vasoconstriction.

The differentiation between the various forms of essential hypertension is of great importance in prognosis. Whereas the benign type may be present for several years without causing serious complications in patients with malignant hypertension, death usually occurs from congestive heart failure, cerebral hemorrhage, uremia, or a combination

of these causes within two years after the diagnosis is made. All types of essential hypertension have been observed occasionally in young individuals, but they occur most commonly in persons more than 45 years of age. The relationship to age is at times of importance in distinguishing between essential hypertension with renal insufficiency and chronic glomerulonephritis wth hypertension but cannot be taken as an absolute guide.

Hypertension Due to Glomerulonephritis

Arterial hypertension is a common feature of acute diffuse glomerulonephritis and may even precede the appearance of edema and other characteristic signs of the disease. The pressure usually returns to normal as the evidence of active nephritis subsides; when the elevation persists, it may be interpreted as evidence that the disease is progressing to the subacute or chronic phase. The differentiation between essential hypertension and acute glomerulonephritis with hypertension offers no difficulty. The clinical history, the presence of edema, and the urinary findings, particularly hematuria, serve to establish the diagnosis of acute glomerulonephritis with certainty.

Although chronic glomerulonephritis usually is accompanied by hypertension, the blood pressure may remain within the limits of normal for a considerable period of time in the so-called nephrotic type in which edema dominates the clinical picture. In patients in whom nephritic hypertension has been present for some time, ophthalmoscopic examination may reveal findings which are indistinguishable from those observed in any of the three types of essential hypertension. The differentiation between typical cases of chronic glomerulonephritis and essential hypertension usually is easily made. A history of former acute glomerulonephritis is of primary importance but in many patients cannot be obtained either because the illness occurred so many years earlier that it has been forgotten or because the attack was so mild that it passed unnoticed.

Chronic glomerulonephritis occurs in individuals of all ages, but, in contrast to essential hypertension, it is relatively uncommon after the age of 45 years. The most valuable clinical signs of chronic glomerulonephritis are the presence of diminished renal function, albuminuria with urinary casts and microscopic hematuria, edema of renal origin, and anemia. These findings serve to distinguish the disease immediately from those cases of essential hypertension in which renal function has not been impaired. When the same findings are encountered, however, in a patient between 30 and 45 years of age, it may be impossible to determine, in the absence of a history of earlier acute nephritis,

whether the condition is chronic glomerulonephritis or essential hypertension which has progressed to the stage of producing marked impairment of renal function. A similar clinical picture in individuals less than 30 years of age will usually be the result of chronic glomerulonephritis, while in patients past the age of 45 years, essential hypertension is the most probable cause.

The actual height of the blood pressure is of comparatively little value in differential diagnosis, but extremely high pressures are more common in essential hypertension than in chronic glomerulonephritis. Although the heart becomes hypertrophied from nephritic hypertension of long duration, congestive myocardial failure occurs in only a small number of patients, and the common cause of death is, of course, uremia.

Hypertension Due to Urinary Obstruction and Polycystic Disease of the Kidneys

Long continued urinary obstruction, regardless of the cause, may produce a constant elevation in arterial pressure. Among the most common conditions which produce hypertension in this way are hypertrophy of the prostate, bilateral renal calculi, and bilateral ureteral obstruction due to malignant disease of the bladder, uterus or cervix. Essential hypertension may occur in patients who have any of these disturbances, and the decision as to whether the elevation in pressure in a particular case is of this type or due to urinary obstruction frequently must be postponed until the obstruction has been relieved.

In the majority of patients with polycystic disease of the kidneys, the blood pressure is elevated, at times to very high levels. Evaluation of the hypertension depends upon recognition of the underlying disease.

Hypertension in Pregnancy

Elevation of the blood pressure during pregnancy may be due to chronic glomerulonephritis, essential hypertension, or toxemia of pregnancy. In patients with chronic glomerulonephritis, hypertension may have been present for some time before conception or, in individuals in whom nephritis is present in the so-called latent stage, it may not develop until pregnancy has progressed for two or three months or even longer. Recognition that the elevated pressure is the result of glomerulonephritis depends upon the presence of albuminuria with microscopic hematuria and casts early in pregnancy, diminished renal function and a history, when obtainable, of earlier acute glomerulonephritis.

Because essential hypertension is relatively uncommon in individuals less than 45 years of age, elevation of the blood pressure during preg-

nancy is seldom due to this condition. When essential hypertension is the cause, the pressure usually will have been above normal for some time before the onset of pregnancy. In order to establish a diagnosis, it is necessary that the renal function be normal or only slightly impaired, since more than slight diminution in function almost always is to be regarded as evidence of glomerulonephritis in patients in the childbearing age. In addition to the small group of individuals in whom essential hypertension complicates pregnancy, patients who are constitutionally predisposed to this type of elevated blood pressure may first show increased tension during gestation, usually in the later months. Following delivery, the blood pressure generally returns promptly to normal, but after a period of a few months to several years, it again becomes elevated[4].

The most common cause of hypertension during pregnancy is that form of toxemia to which the term "kidney of pregnancy" or "low reserve kidney" is applied. This type of toxemia is characterized by the development, in the later months of pregnancy, of elevated pressure, usually of only slight or moderate degree, albuminuria with urinary casts, and edema. In spite of the edema and urinary findings, renal function is normal. The condition may progress more or less rapidly to pre-eclampsia and eclampsia, but usually it is possible to carry the patient to term or at least to the period of viability. Delivery is followed by a prompt return of the blood pressure to normal and disappearance of the albuminuria and edema. There is no evidence that patients who have experienced this type of toxemia are predisposed to the subsequent development of essential hypertension or impaired renal function.

Hypertension Due to Lead Poisoning

Hypertension with elevation of both the systolic and diastolic pressure is a common accompaniment of acute and chronic lead poisoning. In the acute phase of plumbism, the increased tension is the result of vasoconstriction due to the direct action of lead upon the smooth muscle of the arterioles. If the individual has been exposed to lead for but a short time and is subsequently protected against further exposure, the hypertension is usually transitory and the pressure returns to normal as the symptoms of intoxication subside. Prolonged exposure, on the other hand, frequently results in permanent elevation in pressure even though the patient has experienced no symptoms of acute poisoning. In a certain number of these patients, tests of renal function indicate the presence of kidney damage, and postmortem studies reveal renal lesions similar to those observed in patients with essential hypertension

and secondary vascular nephritis. Whether these pathologic changes are the direct result of the action of lead upon the kidneys and are the principal cause of the elevated pressure of chronic lead poisoning has not been determined. They may be but a secondary effect of the hypertension itself. In other individuals who have been subjected to prolonged exposure, the blood pressure is elevated but renal function is normal and no anatomic change can be demonstrated in the kidneys. In these patients it is probable that the increased tension has resulted from the direct effect of the lead upon the blood vessels.

The diagnosis of hypertension due to lead poisoning is established by the history of exposure, the occurrence of symptoms of lead intoxications, and the presence of signs of lead absorption. Of the latter signs, punctate basophilia of the erythrocytes, the gingival lead line, and the presence of lead in the urine are the most important. Lead is excreted from the body principally through the gastro-intestinal tract, but the presence of lead in the feces is of little diagnostic importance unless the possibility of the patient's having ingested lead can be excluded absolutely. The presence of lead in the urine, on the other hand, is absolute proof of earlier lead absorption.

Hypertension Due to Arteriosclerosis

It is a matter of common knowledge that even extreme degrees of generalized arteriosclerosis are encountered frequently in individuals whose blood pressure tends toward the lower rather than the higher limits of normal. In a certain number of patients with advanced arteriosclerosis, however, a moderate elevation in systolic tension is recorded. The characteristic feature of this hypertension and the feature which differentiates it from essential hypertension is that the increased systolic value is associated with a normal diastolic reading [5].

Hypertension in Coarctation of the Aorta

Coarctation of the aorta consists of a localized stenosis or atresia of the descending arch of the aorta at the point of insertion of the ductus arteriosus. One of the most striking features of the condition is the development of collateral arterial circulation between the branches of the aorta above and below the site of stenosis. This is accomplished mainly by the following routes: (1) by anastomoses between the superior intercostal artery of the subclavian and the first aortic intercostal arising from the aorta below the site of the constriction, (2) by anastomoses between the aortic intercostal arteries and the subscapular artery and its branches, particularly the circumflex scapulae, and (3) by anastomoses between the internal mammary and the deep epigastric arteries. The extent to which each of these vessels takes part in the

collateral circulation varies considerably in different patients. The collateral circulation may manifest itself clinically by the presence of pulsating vessels over the back, epigastrium, and lower anterior part of the thorax, prominent subclavian and subscapular arteries and palpable deep epigastric arteries. In addition, roentgenographic examination of the thorax reveals erosions of the inferior borders of the ribs bilaterally.

Because of the resistance offered to the flow of blood by the stenosed aorta and the collateral arterial pathways, patients with coarctation present hypertension in the vessels of the arms and relatively low blood pressure in the legs. In addition, the femoral pulse wave often is retarded and diminished in amplitude or even absent. This diagnostic sign is seldom absent, and because its presence immediately suggests coarctation of the aorta, the femoral pulse should be palpated in all individuals with elevated brachial blood pressure.

Hypertension Due to Pituitary Basophilism and Tumors of the Adrenal Cortex

Cushing[6], in 1932, described a syndrome due to basophilic adenomata of the pituitary gland in which hypertension is a constant finding. The syndrome usually occurs in young adults and, in addition to the increased blood pressure, is characterized by the rapid development of obesity which is frequently painful and is confined to the face, neck, and trunk, by purplish abdominal striae, and softening of the bones which often leads to marked kyphosis due to collapse of the vertebral bodies. In females, amenorrhea and hypertrichosis of the face and trunk develop early. Hyperglycemia and glycosuria are common findings, and the patients frequently have a dusky or plethoric appearance. The erythrocyte count is often increased, the skin at times is extremely dry, and purpuric manifestations have been described. The patients seem to be very susceptible to infections, particularly of the respiratory tract. The symptoms of the malady appear to result in part from disturbances in the function of the anterior lobe of the pituitary gland, and in part from secondary effects upon the thyroid and parathyroid glands, and the pancreas, and the suprarenals. The suprarenal glands[7] usually are found to be hypertrophied at autopsy, and in a few cases an adenoma of the adrenal cortex has been present.

Although pituitary basophilism is not common, the syndrome is of considerable importance because of its possible bearing upon the entire problem of essential hypertension. The pituitary body has been mentioned frequently in discussions on the etiology of essential hyperten-

sion, and the Cushing syndrome supplies a definite example of a relationship between the pituitary and elevated blood pressure.

It has been recognized for many years that tumors of the adrenal cortex may be responsible for the development of a symptom complex in which hypertension occupies a prominent place. The clinical picture which results from these neoplasms may be indistinguishable from that of pituitary basophilism. It is quite possible that in some of the earlier cases reported as instances of adrenal tumors causing hypertension, Cushing's syndrome was really present but was not recognized because of inadequate examination of the pituitary body. Recently, however, cases have been reported in which all the features of pituitary basophilism have been associated with an adenoma of the adrenal cortex and a perfectly normal hypophysis[8].

Summary

This discussion has been limited to a consideration of those forms of hypertension which are encountered most frequently in clinical practice or are of special interest because of their possible bearing upon the problem of the etiology of essential hypertension. That an elevation in blood pressure is observed either as a transient or sustained phenomenon in several other conditions is well known, but in these states the increased tension either is an unimportant part of the clinical picture or is encountered so uncommonly as to warrant omission from consideration at this time. Differentiation of the various types of hypertension is of fundamental importance with respect to treatment and prognosis, and one is always amply repaid for whatever effort he may expend in attempting to arrive at a proper classification in a particular case.

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BUMPER FRACTURE OF THE KNEE

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and

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In 1929, Cotton and Berg[1] coined the name bumper fracture for the injury caused by the impact of the automobile bumper against the outer aspect of the extended knee. Their definition reads in part: "This is the fracture of the outer side of the tibial head, produced by abduction of the leg forcible enough to smash the external tuberosity against the fulcrum of the outer condyle of the femur." Many articles have been written on this subject since then, but there still exists considerable difference of opinion as to the most desirable method of treatment. In this brief communication we wish to discuss some of the problems involved and outline a plan of treatment that has aided us materially in preventing the knock-knee deformity which so commonly occurs.

The violence sustained is of the crushing type and, if severe, leaves the knee with a squashed, depressed, comminuted, external tibial condyle. On examination, the most characteristic finding is the marked lateral instability of the joint which permits the leg to be abducted on the thigh to a varying extent. The external semilunar cartilage may be dislodged or even forced down between the condylar fragments. The tibiofibular joint is disrupted and the head of the fibula is sometimes crushed. The external and internal lateral ligaments are torn or remain intact, depending on the severity of the injury.

Many different methods of reduction, both open and closed, have been devised. In principle, all these seek to obtain restoration of an even tibial articular surface and to correct the knock-knee deformity. Even with a minor amount of persistent depression of the external condyle, the knee will be forced into a valgus position when weight bearing is started, and the entire limb will be thrown out of proper alignment. The type of reduction adopted will depend on the exact nature of the fracture and to determine this accurately, it is necessary to have multiple roentgenograms which are made not only in the anteroposterior and lateral positions, but also at quarter angles. With the aid of these, the fracture may be classified in one of three groups according to the following simple scheme:

1. Those in which the condyle has been displaced mainly in a lateral direction (squash fracture).

2. Those in which the condyle has been displaced mainly in a downward direction without extensive comminution (depression en masse).

3. Those in which the condyle has been comminuted and depressed.

For the first class, closed reduction is indicated. This may consist of pounding the condyle with a mallet in an upward and inward direction or compressing the site with a carpenter's wood clamp fashioned after Boehler's redresseur for calcaneal fractures. Great caution should be exercised to avoid injury to the soft parts, especially the common peroneal nerve. The reduction may be carried out immediately or after a week or ten days. The latter has the advantage of allowing organization to proceed to the stage when the fragments are more likely to remain in position. The leg should then be immobilized with the knee in varus.

For the second class, closed reduction may be tried if there is only a single fragment, but open operation will give better results in the majority of cases.

For the third class, and unfortunately most cases are in this group, open operation gives the best chance of preserving optimum joint function. The problem is, first, to elevate the depressed fragments so that the external condyle is on a level with the internal condyle and, secondly, to maintain the fragments in the corrected position.

The details of the operation will depend on the findings. The fracture site is approached through a longitudinal incision along the lateral aspect of the knee. The contour of the condyle should be reëstablished by elevating the crushed bone with a dull chisel, periosteal elevator, or similar instrument, until the articular surface is even and level. When the comminution is extensive, it may be necessary to insert bone chips or a single solid graft taken from the crest of the tibia. An attempt should be made to save the external semilunar cartilage but there are cases in which this has to be sacrificed. This in itself need not be a source of disability since it is well known that joint function is not necessarily dependent on the presence of the semilunar cartilages.

In fractures of the second class and in the less extensively comminuted fractures of the third class, the depressed fragment or fragments may be retained in position by a suitable peg or screw. Some surgeons have suggested passing a small bolt from the lateral to the medial side of the tibia to obtain compression, but we have not found it necessary to resort to this procedure.

Just as important as the need of accurate reposition is that of main-

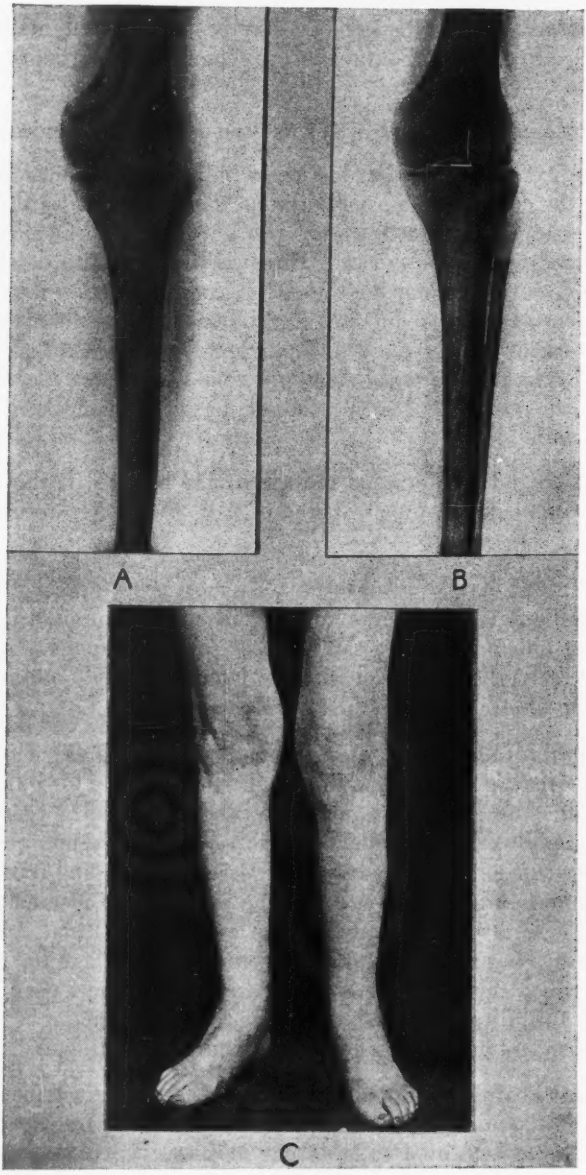

FIGURE A.—Before reduction. Squashed comminuted fracture of external condyle with marked outward displacement.

FIGURE B.—Five months after reduction. Outward displacement corrected. Tibial articular surface even and level.

FIGURE C.—The fracture occurred in the left knee. There is no valgus deformity and the knee has active, painless motions from complete extension to well over 90° flexion.

taining the reduction, and it is here that, in our opinion, many errors occur. During the operation and the application of the plaster cast, the knee must be forced into the maximum varus position. Particularly in cases with marked comminution, we have frequently found that, in spite of strict precautions, some depression of the condyle would recur and subsequent roentgenograms would show to our chagrin that less correction existed than had been accomplished at operation. This was in all probability due to the inavoidable handling of the limb while the cast was put on. Such an occurrence can easily change the outcome of an otherwise carefully planned operation. For that reason we have adopted the following technique which has been exceedingly helpful in preventing any untoward postoperative displacement.

After roentgenograms have been taken and operation has been decided on, the knee is manipulated into the maximum varus position and a cast applied, reaching from the trochanters to the toes. The cast is then allowed to harden and a large window is removed from the outer side, exposing the lateral aspect of the knee. The operation, according to the indications mentioned above, is then carried out through the window. It has given us a sense of confidence to know that when the comminuted fragments are replaced, they will remain in position without any chance of shifting by inadvertent movements. We also believe that this method minimizes the need for the various types of pins and screws that have been used.

The accompanying illustrations show the roentgenograms as well as the postoperative result of a typical case treated by this method.

Plaster protection is continued for a period of eight to ten weeks and after this time active motion is started. Weight bearing is postponed for another two weeks, and then the limb should be protected for at least several months by means of a Thomas walking caliper with a leather cuff to support the knee in varus.

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INTRACRANIAL METASTASIS AS EARLIEST EVIDENCE OF CARCINOMA OF THE LUNG

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During the past four years it has been my experience in two cases to disclose metastatic carcinomatous lesions of the brain unexpectedly at operation. At autopsy later on these were shown to have originated from primary bronchogenic carcinoma of the lung. In both cases the final preoperative diagnosis was primary brain tumor. Although a metastatic lesion of the brain was suspected in Case I, no primary tumor could be revealed by a most exhaustive clinical investigation; in fact, the primary site of the tumor in this case was not revealed until autopsy, one year and ten months after the intracranial operation. In the second case, the presence of a metastatic lesion of the brain was not suspected until the ventricular cannula encountered unusual brownish mucoid material deep in the brain substance during the operation of ventriculography. Chiefly because of the diagnostic problems presented by these cases, it has been considered worth while to report and discuss them in some detail. Surgical therapy in such cases will also be discussed briefly.

Case 1: A white woman, aged 49 years, was referred to the Clinic on January 11, 1932, by Dr. J. S. Zimmerman of Youngstown, Ohio. Her chief complaints were "pains in the head" and vomiting. She had been in good health until the summer of 1931, when she began to have suboccipital headaches which lasted for an hour or two and recurred about once a week. The headaches became more frequent and more severe, and in November, 1931, they were accompanied by nausea, vomiting, and blurring of vision. After November, 1931, suboccipital headaches occurred in bouts lasting only a few minutes and subsiding rapidly. These bouts recurred as often as ten times daily and were usually accompanied by vomiting. At such times there were occasional, momentary lapses of consciousness, but no prolonged coma. The attacks were described as "sudden blinding attacks of headache." No convulsions, paralysis, dizziness, deafness, or staggering occurred, and there had been no cough, dyspnea, hemoptysis, or pain in the chest.

General physical examination revealed a weak, anemic woman with sallow, dry skin. The pulse rate was 100 and the blood pressure was 116 systolic, 66 diastolic. There was no evidence of cardiac, pulmonary, or intra-abdominal disease. Pelvic and rectal examinations revealed no abnormalities.

Neurological examination was entirely negative except for diminished corneal reflexes in both eyes. Vision 6/30 O.D.; 6/30 plus 1 O.S.

Ophthalmoscopic examination revealed definite edema of both discs, 1.5 diopters O.D. and 2.5 diopters O.S. There were some hemorrhages in the left retina and the vessels were tortuous. Examination of the visual fields showed enlargement of both blind spots. The patient did not coöperate well during this examination.

Otolaryngological examination showed no abnormality in the nose, throat, larynx, or ears.

Laboratory work: The skull was reported to be normal by roentgen examination. Lumbar puncture obtained clear, colorless, cerebrospinal fluid under normal pressure and there was no block as shown by the Queckenstedt test. Examination of the fluid showed three cells, faint trace of globulin, 50 mg. total protein, negative Wassermann and Kahn reactions, colloidal gold curve 2-2-2-1-1-1-0-0-0-0. Urinalysis showed no abnormalities and the blood Wassermann reaction was negative. Examination of the blood showed 3,780,000 red cells, 9,650 white cells, and 71 per cent hemoglobin.

After completion of the above examinations, a tentative diagnosis of unlocalized brain tumor was made. Because of the fact that the general appearance of this patient suggested that a cryptic malignancy might be present elsewhere in the body, it was considered advisable to carry out the following examinations in an effort to locate a primary tumor from which an intracranial metastasis might have arisen:

Roentgen examination of the chest showed no evidence of pulmonary neoplasm or abscess.

Roentgen examination of the gallbladder and of the entire gastro-intestinal tract showed no abnormality.

Gastric analysis showed no free hydrochloric acid.

On January 18, 1932, in an effort to localize the brain lesion, ventriculography was carried out. This revealed a moderate, symmetrical dilatation of both lateral ventricles and of the third ventricle, suggesting a subtentorial lesion.

Operation was performed on January 19, 1932. Cerebellar exploration revealed marked herniation of the cerebellar tonsils through the foramen magnum. On the posterolateral surface of the left cerebellar hemisphere, there was a firm, greyish red area of tumor tissue which was adherent to the overlying arachnoid and dura. There was no evidence of tumor in the fourth ventricle or in the right cerebellar hemisphere. Using the electrosurgical cutting loop, the tumor in the left hemisphere was removed piecemeal. As this procedure continued, the reddish tumor could be traced into the interior of the cerebellum. In some places it appeared to infiltrate the cerebellar substance slightly and in other places it was possible to find a plane of cleavage between pathological and normal tissue. A mass of tissue about the size of a lime was then removed until the walls of the cavity showed the appearance of normal cerebellar tissue. Following this procedure, fluid flowed freely from the fourth ventricle, which previously had been obstructed by the pressure of the tumor in the left cerebellar hemisphere. The wound was closed, leaving the usual adequate decompression of the posterior fossa of the skull.

The patient's postoperative course was smooth and uneventful, and she was discharged from the hospital on the twenty-first day after operation. At that time she was free from headache and was able to use all extremities without ataxia.

Pathological Report (Dr. Allen Graham): Microscopical examination of section of tumor mass from cerebellum shows masses of edematous, hemorrhagic, cerebellar tissue, with large quantities of foam-cells in some areas. There is a tumor mass consisting of alveolar and pseudoglandular structures. The periphery of these consists of a sharply outlined layer of elongated, columnar

cells, with relatively small, round, deeply staining nuclei, separated at the base and resting on a sharply defined stroma. The opposite end of the cell is finely granular and seems to have vacuoles. In some areas, these cells, in single layers, form spaces suggestive of glandular structure. In other areas, the space is filled by a solid mass of these cells, which are of polygonal shape, have considerable pink-staining, reticulated cytoplasm, with many vacuoles, and round or oval, deeply staining, richly chromatic nuclei. The tumor cells seem to be secreting a mucoid material. *Diagnosis:* Tumor of cerebellum, probably metastatic.

Subsequent Course: Two months later the patient was free from headaches, her vision had improved, and she was gaining strength. Examination showed no neurological abnormalities. There was no ataxia or nystagmus, and there was complete recession of papilledema. The patient's progress was favorable for nine months, during which time she was free from headaches and vomiting, although she failed to gain weight and continued to appear thin and emaciated. Then she began to lose ground and had occasional headaches, vomiting, and mental confusion. In October, 1932, examination of the eyes showed a choked disc of one diopter in each eye, and lumbar puncture showed clear, colorless fluid under increased pressure (240 mm.). The spinal fluid contained five cells, a marked trace of globulin, and 48 mg. total protein. It was evident that the intracranial pressure was moderately increased, perhaps due to recurrence of the tumor. Another operation, however, was not considered advisable at that time.

At home the patient declined from October, 1932, to January, 1933, and she was in a semi-stuporous condition much of the time. From January to July, 1933, temporary improvement was noted; there was no headache or vomiting, and although the patient was mentally clouded, she was able to stand on her feet, ask for food, recognize friends, and go for automobile rides. After July, 1933, she was confined to her bed until the time of her death, November 18, 1933. During this final period, she could not feed herself, her consciousness was greatly clouded, she became weak and lost weight, and weakness of the left arm and contracture of the left leg developed. On November 5, 1933—two weeks before death—she was observed at her home, where she lay in bed, greatly emaciated, with spastic paralysis of the left arm and left leg, and unable to eat or speak. She appeared to be awake and conscious, but lay motionless in bed, having the appearance of a cadaver in whom cardiac contractions seemed to be the only objective evidence of life. Obviously, the patient was dying from extensive recurrence of the intracranial tumor. Death occurred quietly November 18, 1933, twenty-two months after operation.

Autopsy, November 19, 1933: In the upper lobe of the left lung, contiguous with a bronchus, there was a firm tumor, which measured 2 x 1.2 cm. in diameter. A second small nodule was found on the external anterior surface of the left upper lobe. Microscopic examination showed a bronchogenic carcinoma. The peribronchial lymph nodes on the left side were also involved. Examination of the brain revealed a large metastatic tumor 6 cm. in diameter on the inferior surface of the right frontal lobe which caused marked compression and distortion of both frontal lobes. The tumor did not invade the left hemisphere. In the right hemisphere the tumor was partially degenerated and cystic, containing thick, mucinous material. There was a small cortical tumor nodule, 8 mm. in diameter, on the inferior surface of the right temporal lobe. Grossly, the

cerebellum showed no recognizable tumor tissue. Sections from the tumor masses in the right frontal lobe, right temporal lobe, and fragments of tissue from the left cerebellar hemisphere showed an adenocarcinoma, similar in all respects to the lesion in the lung and to the tumor which had been removed surgically from the cerebellum twenty-two months before. Therefore, it was our opinion that the original tumor of the cerebellum, as well as the later intracranial recurrences, were all metastatic from the small bronchogenic carcinoma of the left lung.

Discussion of Case 1: The outstanding features of this case are (1) the diagnostic difficulty, (2) the prolonged survival of the patient, and (3) the large size of the intracranial metastases in comparison with the small primary lung tumor.

Although a primary neoplasm in another location was suspected, the lung tumor in this case caused no symptoms or signs, and it was apparently too small to produce a shadow in the roentgen film. Here cerebral metastasis gave rise to the earliest symptoms of the disease.

The survival of this patient for twenty-two months after operation for carcinomatous metastasis to the brain seemed quite surprising to the writer, although Cushing[1] called attention to long postoperative survival periods (five and one-half years, three years, and two years) in such cases. Although this patient was neither a useful nor companionable citizen during the last half of her postoperative course, at least she was free from severe head pain and vomiting.

Case 2: A white man, aged 48 years, was referred to the Clinic February 2, 1936, by Dr. John D. O'Brien of Canton, Ohio. A diagnosis of intracranial tumor had been made. The patient apparently had been in good health until November, 1935, when severe frontal headaches developed which were thought to be due to "frontal sinusitis" or "neuralgia." The headaches gradually became more severe, occurring at times in the temporal and occipital regions, and they were occasionally accompanied by nausea. In December, 1935, failing vision and dizziness were first noticed, and the patient's glasses were changed without relief of headaches. The symptoms became steadily more severe, and the gait became unsteady. He had been in bed for three weeks prior to admittance at the Clinic. He had noticed occasional numbness of the right leg and at times he had difficulty in finding the desired words for vocal expression. There had been no convulsions, paralysis, cough, dyspnea, hemoptysis, or pain in the chest.

General physical examination revealed a somewhat emaciated adult white man who was apparently well oriented and coöperative. The pulse rate was 82 and the blood pressure was 150 systolic, 100 diastolic. There were no signs of pulmonary, cardiac, or intra-abdominal disease. The prostate was normal in size and consistency.

Neurological examination showed sixth nerve palsy of the right eye, sluggish tendon reflexes throughout, absent patellar reflexes, unsteady gait, positive Romberg sign, and transient aphasia.

Ophthalmoscopic examination showed bilateral choked disc, 6 diopters, O.D.; 5 diopters O.S.

Examination of the visual fields could not be made because of inability of the patient to coöperate.

Laboratory work: Urinalysis revealed no abnormalities. Examination of the blood showed 5,280,000 red cells, 9,100 white cells, and 81 per cent hemoglobin. The blood Wassermann test gave a negative reaction. Examination of the cerebrospinal fluid which was obtained from the right lateral ventricle at operation later showed no cells, no globulin, 20 mg. total protein, negative Wassermann reaction, and negative colloidal gold test. Roentgen examination of the skull showed marked demineralization of the clinoid processes.

A preoperative diagnosis of probable cerebellar tumor was made and it was planned to do ventriculography followed by intracranial exploration as indicated by the roentgen findings.

Operation was performed January 5, 1936. The posterior horn of the right lateral ventricle was tapped through the usual drill hole and 25 or 30 cc. of clear, colorless cerebrospinal fluid was obtained under pressure. On attempting to insert a cannula into the posterior horn of the left lateral ventricle, a cystic cavity was encountered at a depth of 5.5 cm. in the left occipital lobe, and thick, brownish, syrupy, mucinous material escaped from the end of the cannula. This fluid was darker and more viscous than that usually seen in gliomatous cysts. Because of the peculiar character of the fluid, it was thought that there might be a metastatic lesion in the left occipital lobe. Air was injected into the right lateral ventricle and roentgen films were made. These showed a marked shift of the ventricular system from the left to the right side of the head. The right lateral ventricle and the anterior horn of the left lateral ventricle were considerably dilated. The posterior horn of the left lateral ventricle was obliterated. It was evident that there was a large space-filling lesion in the left occipital lobe.

Because it was thought that there might be a metastatic lesion from a lung tumor, a single flat roentgen film of the chest was made while the patient was under avertin anesthesia. This film failed to show evidence of a lung tumor.

A left occipital craniotomy was then done, and after revealing the presence of a large subcortical tumor, the whole left occipital lobe was amputated with the electrosurgical unit. Two hours after operation, the wound was reopened in order to deal with intracranial hemorrhage, but in spite of control of bleeding from the dural veins, artificial respiration, and various stimulants, the patient expired during closure of the wound.

Autopsy revealed a small carcinoma of the left main bronchus and a larger tumor nodule, 2.5 cm. in diameter, in the apex of the left lung, with metastasis to the bronchial lymph nodes. There was a cystic metastatic nodule, 3 x 2.5 cm., in the cerebellum, but no more nodules in the cerebrum. The cystic cavity contained brown, mucinous material. Microscopic examination revealed the same histological picture of bronchogenic adenocarcinoma in the surgical and postmortem sections.

Discussion of Case 2: In this case the preoperative diagnosis was probable cerebellar tumor, primary in the cerebellum. The possibility of a metastatic tumor of the brain arising from a primary tumor elsewhere had been entirely overlooked because of the complete absence of symptoms and signs of such a primary growth. There was nothing in the history or in the physical examination to suggest the presence of a primary lung tumor. Such a lesion was not even considered until the ventricular cannula encountered thick, brown, mucinous material in the left occipital lobe; after this finding, a belated and not entirely satisfactory roentgen film of the chest failed to reveal evidence of the lung tumor.

The massive obliteration of the posterior horn of the left lateral ventricle as revealed by the ventriculograms overshadowed in diagnostic importance the general dilatation of the remainder of the left ventricle and the right ventricle and indicated the advisability of operation in the left occipital lobe. Armed with the knowledge of a cerebellar metastasis found at autopsy, it can be said in retrospect that the general dilatation of the ventricles was unquestionably due to obstruction to the outflow of fluid from the fourth ventricle. In the future, ventriculographic evidence and clinical data similar to those found in Case II should suggest the likelihood of multiple lesions of the brain.

General Discussion

In both cases reported, the primary lung tumor was "silent," subjectively and objectively, and even roentgenographically. Symptoms and signs of intracranial tumor were preëminent. Bailey[2] wrote, "Primary bronchogenic carcinoma of the lung so commonly metastasizes to the brain and does it so often before the primary tumor has given symptoms, that it should always be looked for in any patient of middle age, or beyond, who develops rather rapidly symptoms of an infiltrating tumor of the brain." He advised roentgen examination of the chest whether or not pulmonary symptoms were present. Grant[3] reported a case of cerebral metastasis from a lung cancer, which was entirely unsuspected until histological examination of the brain tumor which had been removed at operation revealed the nature of the lesion. Then roentgen examination of the chest was made and this showed evidence of a large lung tumor. Grant stated that the most common primary foci for carcinomatous metastasis to the brain were the breast and lungs. Meagher and Eisenhardt[4], in studying forty-four metastatic intracranial carcinomas in Cushing's series, found that 35 per cent of these lesions originated in primary lung tumors while 25 per cent originated in breast cancers. Fried and Buckley[5] reviewed thirty-eight cases of proved

primary carcinomas of the lung, and found surgical or postmortem evidence of intracranial metastasis in fifteen cases. In the other twenty-three, either there were no metastases to the brain or the brain was not examined. These authors stressed the insidious course of the disease and the frequent occurrence of symptoms and signs of brain metastases as the earliest evidence of primary lung tumor. In eleven of their fifteen cases, the clinical diagnosis was primary tumor of the brain, and lung tumor was overlooked. Rogers[6] found in fifty cases of primary cancer of the lung that the initial symptoms were cerebral in 14 per cent of cases, and he called attention to the high incidence of intracranial metastases from such neoplasms. Elkington[7], in a study of seventeen cases of metastatic tumors of the brain, found that these tumors were secondary to primary carcinoma of the bronchus in nine cases (52.9 per cent). He recommended roentgen examination of the chest in all cases of cerebral tumor of recent onset in elderly people and in all cases of obscure brain disorders suggesting multiple lesions.

From a diagnostic standpoint, then, it is important to bear in mind the possibility of a primary lung tumor in all cases of brain tumor, particularly in patients over 40 years of age. Even in the absence of positive physical and positive roentgen signs, the presence of a primary lung tumor cannot be excluded, because it may be so small or so peculiarly situated as to produce no shadow roentgenographically.

Surgical Therapy

Patients harboring intracranial malignant metastases often suffer from severe headache. Postoperative survival periods have been surprisingly long in some cases. Oldberg[8] reported a postoperative survival period of more than two years in two cases and eight months in another case and gave excellent reasons for suggesting operation on suspected malignant metastases to the brain. Elkington[7] recommended decompression for the relief of headache in such cases.

Cushing[9] stated that operations in such cases "may not infrequently afford a vast degree of symptomatic relief for which patients and their relatives are most grateful. Hence when the unfortunate victims of these disorders once come to be admitted to the hospital wards, it is difficult to refuse their appeals to give them at least the chance of temporary palliation of symptoms which a decompression may afford."

The writer can only agree heartily with the surgical judgment so expressed. Operation should not be performed, of course, when the patient is in poor general physical condition. In addition to decom-

pression as a palliative measure for relief of pain, occasionally, as pointed out by Oldberg[8], it may be possible to remove a single metastatic lesion with prolongation of the patient's life expectancy.

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FURTHER OBSERVATIONS ON THE EXPERIMENTAL PRODUCTION OF URINARY CALCULI*

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In previous communications,[1,2,3] it has been demonstrated that if white rats were maintained for a period of time on a diet deficient in vitamin A, urinary calculi would develop in a large percentage.

In our researches, it was found that when animals were fed a diet deficient in vitamin A for a period of 250 days, postmortem study revealed the presence of vesical calculi in 88 per cent and of renal calculi in 42 per cent of the animals. It likewise was shown that if vitamin A alone were added to the deficiency diet, the formation of calculi was prevented. After the presence of calculi, which were too large to pass spontaneously from the kidney or bladder of the rats, had been demonstrated roentgenographically, an excess of vitamin A was added to the deficiency diet, and in every instance, provided the experimental animal survived, the calculus then underwent spontaneous solution and disappeared. This solution occurred in a comparatively shorter length of time when a co-existing urinary infection was not present. The calculi produced in this experimental work varied in diameter from 0.5 to 12 mm. They were light brown in color, spherical in shape, and they were composed chiefly of calcium phosphates with traces of carbonates. No oxalates or uric acid were present. A small amount of mucoid substance was noted also.

After these researches, the question arose as to whether the chemical constituents of the calculi could be changed by altering the diet. As reported previously, a decrease in the phosphorus in the diet in relation to the calcium caused a complete reversal in the chemistry of the stone, and under these circumstances the principal constituent of the stones was then calcium carbonate. Traces of calcium and magnesium phosphate were found. Traces of oxalates were present, but no uric acid was found.

The question which then presented itself was: "Why can uric acid calculi not be produced in the white rat by further modification of the diet?" The absence of uric acid in the calculi produced in the white rat may, of course, readily be explained by the fact that these animals possess the power of oxidizing approximately 80 per cent of the circulating purines to allantoin. Allantoin is much more soluble in water than uric acid and thus it never forms a constituent of the calculi in rats.

It has been stated that calculi have been produced experimentally only in white rats—a species quite remote phylogenetically from man.

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Therefore, a similar series of experiments with dogs has been in progress for the past year. In the dog, as in the rat, care must be taken to maintain a mild deficiency diet for a long period of time. If more than a moderate degree of vitamin A deficiency is continued, the animals die from pulmonary complications or from diarrhea—a disease which simulates distemper (Fhloring[4]). Thus, only a very mild degree of vitamin A deficiency is permitted for a long period. Such symptoms as loss of weight, xerophthalmia, and marked weakness of the legs should not occur.

A group of seven dogs has been maintained on the vitamin A deficiency diet for a period of eleven months. Recently, under ether anesthesia, cystotomy was performed on each of four of these animals. Multiple stones were found in the bladders of three, and no stones or sand were noted in the fourth dog. One large stone which was too large to pass spontaneously was allowed to remain in the bladder of each of the three dogs and the bladder was closed by the usual technic. The dogs are now being fed a high vitamin A acid-ash diet in order that we may ascertain whether the stones will undergo solution.

Chemical analyses of the calculi removed from these dogs revealed that they were composed of ammonium and calcium phosphate with small amounts of carbonates. No urates or uric acid were present. Although this series of experiments is too small to warrant definite conclusions, at least we may infer that bladder calculi may be produced in dogs maintained on a mild vitamin A deficiency diet for a considerable period of time.

The possibility of producing calculi composed of uric acid and urates was then considered. It is well known that birds eliminate uric acid and that a greater part of the urea is converted into uric acid. Benedict and Behré[5] discovered the unique mechanisms of uric acid metabolism in pure bred Dalmatian dogs by which considerable uric acid is eliminated in the urine. Investigations are now in progress in our laboratories in an attempt to produce calculi in this animal. Emmett and Peacock[6] in 1923 learned from autopsy findings that avitaminosis in chicks was associated with the presence of urates in the kidneys and at times on the surface of the heart and spleen.

Cruickshank, Hart and Halpin[7] found kidney lesions in practically all chickens that died during their experiments with avitaminosis. The kidneys were pale and contained an accumulation of urates. Likewise Elvehjem and Neu[8] reported an elevation of the blood urea when the chicks were maintained on a diet deficient in vitamin A.

Therefore, we used the following diet in a series of experiments with twenty chickens:

58 parts ground white corn	1 part precipitated calcium carbonate
25 parts wheat middlings (standard)	1 part precipitated calcium phosphate
12 parts crude casein	2 parts dried yeast
1 part sodium chloride	water ad libidum

Irradiation was administered for twenty minutes three times a week. The control chickens were fed green yellow corn instead of white corn. In the test animals, the white corn was replaced occasionally by yellow corn in order to maintain only a slight deficiency for a long period of time. The growth curves and symptoms were indicative of mild deficiency. At intervals, the birds were allowed to progress to the stage in which they developed a staggering gait, ruffled feathers and weakness of the legs. No xerophthalmia was noted.

At autopsy five months later, the kidneys were found to be somewhat pale, urates and sand were present in the kidneys, and the ureters contained urates and small uric acid calculi. Hard concretions of uric acid were present in the cloaca. The blood uric acid in the controls averaged 5.1 mg. per hundred cubic centimeters of blood and after the birds studied had been on the deficiency diet for a period of five months, just prior to postmortem study, the blood urea averaged 14 mg. per hundred cubic centimeters of blood. In order to produce calculi similar to vesical stones, a colostomy has been performed in chickens thus diverting the fecal stream and utilizing the lower segment of the bowel and the cloaca as a bladder. From this structure, small calculi can easily be removed for chemical examination which has shown that they were composed purely of uric acid and urates.

In conclusion, while an insufficient number of dogs and birds has been studied to warrant definite conclusions, the relationship between vitamin A deficiency and the formation of calculi seems probable and the mechanism probably is similar to that which occurs in the white rat.

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